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Program in the History of the Biological Sciences and Biotechnology

Herbert L. Heyneker, Ph.D.

MOLECULAR GENETICIST AT UCSF AND GENENTECH, ENTREPRENEUR IN BIOTECHNOLOGY

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2002

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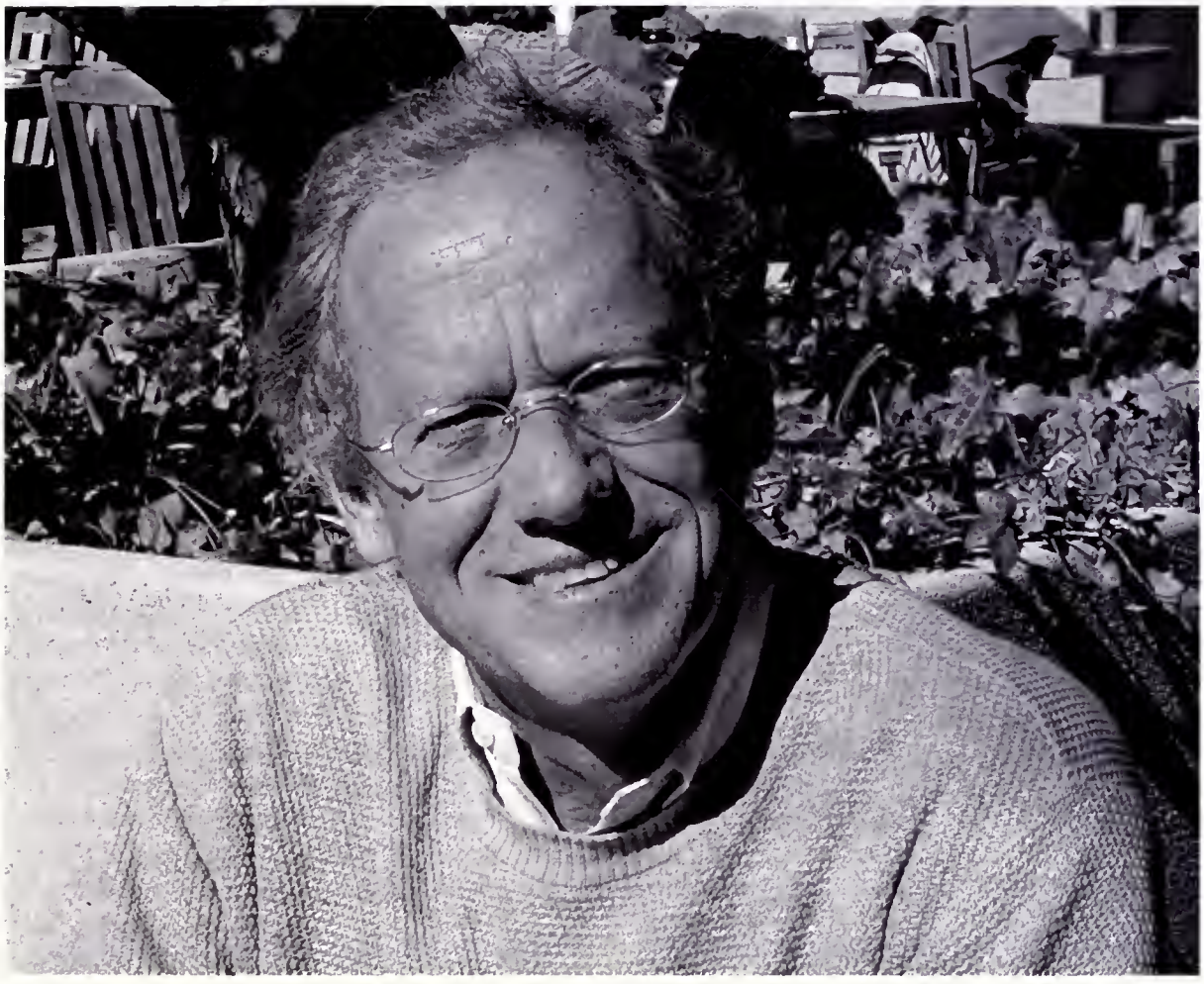

Herbert L. Heyneker, 2003

photo courtesy of Herbert L. Heyneker

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BIOTECHNOLOGY SERIES HISTORY

Genesis of the Program in the History of the Biological Sciences and Biotechnology

In 1996 The Bancroft Library launched the Program in the History of the Biological Sciences and Biotechnology. Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. Yet, although the university is located next to the greatest concentration of biotechnology companies in the world, Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as Bancroft's director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists and the pioneers who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences and generates constant public interest and controversy is vital for a proper understanding of science and business in the late twentieth and early twenty-first centuries.

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history and archival program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in the History of the Biological Sciences and Biotechnology was given great impetus by Genentech's generous pledge to support documentation of the biotechnology industry.

Thanks to these generous gifts, Bancroft has been building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library networks; and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library Web pages.

Oral history as a historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

Emerging Themes

Although the oral history program is still in its initial phase, several themes are emerging. One is "technology transfer," the complicated process by which scientific discovery moves from the university laboratory to industry where it contributes to the manufacture of commercial products. The oral histories show that this trajectory is seldom a linear process, but rather is influenced by institutional and personal relationships, financial and political climate, and so on.

Another theme is the importance of personality in the conduct of science and business. These oral histories testify to the fact that who you are, what you have and have not achieved, whom you know, and how you relate have repercussions for the success or failure of an enterprise, whether scientific or commercial. Oral history is probably better than any other methodology for documenting these personal dimensions of history. Its vivid descriptions of personalities and events not only make history vital and engaging, but also contribute to an understanding of why circumstances occurred in the manner they did.

Molecular biology and biotechnology are fields with high scientific and commercial stakes. As one might expect, the oral histories reveal the complex interweaving of scientific, business, social, and personal factors shaping these fields. The expectation is that the oral histories will serve as fertile ground for research by present and future scholars interested in any number of different aspects of this rich and fascinating history.

Location of the Oral Histories

Copies of the oral histories are available at the Bancroft, UCSF, and UCLA libraries. They also may be purchased at cost through the Regional Oral History Office. Some of the oral histories, with more to come, are available on The Bancroft Library's History of the Biological Sciences and Biotechnology Website: http://bancroft.berkeley.edu/Biotech/.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2002

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1. The three criticisms leveled at oral history also apply in many cases to other types of documentary sources.

January 2004

ORAL HISTORIES ON BIOTECHNOLOGY

Program in the History of the Biological Sciences and Biotechnology
Regional Oral History Office, The Bancroft Library
University of California, Berkeley

Paul Berg, Ph.D., *A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry*, 2000

Mary Betlach, Ph.D., *Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory*, 2002

Herbert W. Boyer, Ph.D., *Recombinant DNA Science at UCSF and Its Commercialization at Genentech*, 2001

Roberto Crea, Ph.D., *DNA Chemistry at the Dawn of Commercial Biotechnology*, 2004

David V. Goeddel, Ph.D., *Scientist at Genentech, CEO at Tularik*, 2003

Herbert L. Heyneker, Ph.D., *Molecular Geneticist at UCSF and Genentech, Entrepreneur in Biotechnology*, 2004

Thomas J. Kiley, *Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur*, 2002

Dennis G. Kleid, Ph.D., *Scientist and Patent Agent at Genentech*, 2002

Arthur Kornberg, M.D., *Biochemistry at Stanford, Biotechnology at DNAX*, 1998

Fred A. Middleton, *First Chief Financial Officer at Genentech, 1978-1984*, 2002

Thomas J. Perkins, *Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995*, 2002

G. Kirk Raab, *CEO at Genentech, 1990-1995*, 2003

Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders (Hugh D'Andrade, David Holveck, and Edward Penhoet), 2001

Niels Reimers, *Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents*, 1998

William J. Rutter, Ph.D., *The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco*, volume I, 1998

Richard Scheller, Ph.D., *Conducting Research in Academia, Directing Research at Genentech*, 2002

Robert A. Swanson, *Co-founder, CEO, and Chairman of Genentech, 1976-1996*, 2001

Daniel G. Yansura, Ph.D., *Senior Scientist at Genentech*, 2002

Oral histories in process:

Moshe Alafi
Brook Byers
Ronald Cape
Stanley N. Cohen
Donald Glaser
Irving Johnson
Daniel E. Koshland, Jr.
Lawrence Lasky
Arthur Levinson
Diane Pennica
George Rathmann
Steven Rosenberg
William J. Rutter, volume II
Axel Ullrich
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto

INTERVIEW HISTORY—Herbert Heyneker

This is a personal story of science and entrepreneurship in the early days of commercial biotechnology. Dr. Heyneker's history begins in Holland, his country of birth and the reason for the slight accent that tinges his fluent English. His trajectory towards applied biology began with his research on DNA repair at the University of Leiden. There he had a portentous encounter with Herbert Boyer, who was making waves in biology circles with his recent development with Stanley N. Cohen of the recombinant DNA technique, and who was willing to make room for the young Dutchman in his UCSF laboratory. In 1975, Heyneker moved his family to San Francisco where he began a two-year postdoctoral fellowship in Boyer's laboratory at UCSF. Not only does Heyneker provide a vivid portrayal of the lab's intense and freewheeling culture at a time when "gene slicing" was the hot thing in molecular biology but also describes his key role in somatostatin research, which became the first project of the fledgling company named Genentech.

By August of 1978 Heyneker had joined Genentech and the handful of scientists who had been lured into the corporate world by the commercial promise of the new genetic technologies. The move was risky on most counts: untried science in a start-up company with no products and no substantial financial backing. But the promise of the science as applied in the production of human pharmaceuticals was too great for Heyneker and his young colleagues to ignore. They turned their backs on the relative calm and security of academia to engage in a venture foreshadowing the growth of a biotech industry in the 1980s.

Heyneker adds substantially to the story told by others in this oral history series of how the combination of recombinant DNA and DNA synthesis capability led Genentech to its first successes with the cloning of the genes for somatostatin (1977), human insulin (1978), and human growth hormone (1979). The youthful team's rare expertise in the new genetic technologies and its scientific drive propelled the projects to success, serving to demonstrate that bacteria could be experimentally induced to produce foreign protein. The work provided the first indications that a company based on recombinant DNA technology might have a commercial future. It was a heady moment for the scientists and perhaps especially for Heyneker, who with his nervous energy and competitive spirit had been key to the somatostatin project from the start. As he succinctly put it: "Somatostatin was the start of a new era" (p.57).

The many stages in Heyneker's professional career and his willingness to talk in detail account for the length of this oral history. In 1984, he left Genentech to join Genencor, Genentech's first spin-off, as vice president of research and development, remaining there a few years before moving on to a series of entrepreneurial ventures which he continues to pursue at the present writing.

The Oral History Process

Twelve interviews were recorded in Heyneker's Victorian in San Francisco. Edgy at first, he warmed to the process when the interviews turned to the science that has been at the center of his professional life. Daunted by the mountainous stack of transcripts sent to him for review, Heyneker thoroughly edited only the first two interviews and hesitated over the remainder. Concerned to finish the project, I agreed to have him review solely those pages where I had questions or otherwise needed his comments. As always with the oral histories supported by Genentech, the transcripts were submitted for review by its legal department. No changes were requested.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is

under the direction of Richard Cándida Smith, Director, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley. The catalogues of the Regional Oral History Office and many online oral histories can be accessed at http://bancroft.berkeley.edu/ROHO/. Online information about the Program in the History of the Biological Sciences and Biotechnology can be accessed at http://bancroft.berkeley.edu/Biotech/.

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Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
January 2004

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Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name HERBERT LOUIS HEIJNEKER

Date of birth 1-22-44 Birthplace AMSTELVEEN THE NETHERLANDS

Father's full name LOUIS HEIJNEKER

Occupation CIVIL SERVANT Birthplace KANSAS City, MI

Mother's full name CATHARINA WILHELMINA STROINK

Occupation _____ Birthplace ENSCHEDE, THE NETHERLANDS

Your spouse/partner PAULINE ELISABETH VAN YSENDOORN

Occupation INTERIOR DESIGN Birthplace BALIKPAPAN, INDONESIA

Your children ① MARC LODEWIJK, ② THYS MAARTEN, ③ PHILIP HARMEN

Where did you grow up? THE HAGUE (DEN HAAG) THE NETHERLANDS

Present community SAN FRANCISCO, CA

Education Ph.D. MOLECULAR GENETICS

Occupation(s) CHIEF TECHNOLOGY OFFICER, EOS BIOTECHNOLOGY
ADVISOR, ABINGWORTH MANAGEMENT

Areas of expertise MOLECULAR BIOLOGY
ENTREPRENEURSHIP

Other interests or activities GOLF, HIKING, TRAVELING

Organizations in which you are active _____

SIGNATURE H.L. Heijneker DATE: 9/30/02

INTERVIEW WITH HERBERT L. HEYNEKER, PH.D.

I FAMILY BACKGROUND

Paternal Grandfather

Adventures in the United States

[Interview 1: March 20, 2002] ##[1]

Hughes: Dr. Heyneker, would you start with your grandparents, and tell me where they lived and what they did?

Heyneker: Okay. I think the history of my grandparents is interesting and relevant for what I do. My paternal grandparents were born in the late 1870s in Amsterdam. My grandfather, Louis Gerardus Frederikus, did not have an academic degree. He probably learned his metier on the job. He became involved with a company in Holland which is called the Deli Maatschappij. This was an organization which did a lot of trading with the Netherlands East Indies, which was at that time a colony of Holland. The Deli Maatschappij was quite a wealthy organization. They, for the time, really became a financial powerhouse. Some of that money was being used to build railroads in the United States. So quite a few railroads here have been funded by European money. The Deli Maatschappij was financially responsible for building the Kansas City Southern Railroad. My grandfather came over to the States in the late 1800s, I would say around 1895, that time frame, and was in charge of overseeing the building of the Kansas City Southern Railroad, which runs from Kansas City to Port Arthur in Texas.

My grandfather was a very adventurous man. Although he did his work, as I mentioned, he also ventured out in other things. He was involved with looking for gold, looking for oil. At one point in time he had a plot of land in Texas, but his friends convinced him that

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1. This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

this was as dry as it could get. Of course, now it turned out to be a very rich oil area. [laughter] But that is all history.

Hughes: So he listened to them and sold the land?

Heyneker: Of course. What I understood from my father, he was sometimes gullible, and if people told him one thing or the other, he followed.

He also was involved as an adventurer to pan for gold in a very commercial way. A consortium my grandfather belonged to had built special boats which could float down the rivers in Montana. They would pan gold that way, with very big trays which would go into the water—so not by hand and sifting through it like this, but on a grand scale.

Hughes: He invented that device?

Heyneker: No, I think he invested in that device. I think he made a lot of money, and he lost a lot of money. He definitely led an adventurous life. He went back to Holland in 1915, 1916, and continued to work for the Deli Maatschappij.

Hughes: He came to the States with his family?

Heyneker: Well, he came here with his wife, Johanna Petronella Elisabeth Klautz. They had two children. The first child passed away after a few weeks, probably because of the heat. In those days it happened a lot.

A Grandson's Associations with a Grandfather

Hughes: Did you know him?

Heyneker: Yes, I did know him. As I said, he came back to the Netherlands in 1915, 1916, and stayed with the Deli Maatschappij. He became the personal secretary for one of the founders/managers of the company. I think he was involved with that company until he retired. Then he lived in Scheveningen, which is very close to The Hague. That's where he passed away, in 1954. I still remember: it was my first funeral, even though I was ten years old. It made a big impression on me.

We saw my grandparents regularly because I lived in The Hague with my family. There was not a whole lot of money around after the war. Often we walked on Sunday to Scheveningen, which was a nice little trek, to visit my grandparents there. We'd have some tea, and we'd either take the bus back or we walked back. So we visited my grandparents on a weekly basis.

Hughes: So you had a chance to know him.

Heyneker: Right, although I probably was too young to ask the true, relevant questions. So I probably learned more from my dad about him than directly from him.

Hughes: Does your grandmother figure in your memory?

Heyneker: Oh sure. After he passed away, she continued to live in the same house for another fifteen years before she passed away. We continued the visiting routine for a while. As she got older, it was reversed; she came to us on Sundays. Yes, my grandparents from my father's side I still remember vividly.

As a matter of fact, if you turn this off—[tape interruption while he gets a framed photo of his grandfather]. I felt that it was a good moment to show you this picture. I'm fond of this. It's on my desk, and I say, "Hey look, I've followed in my grandfather's footsteps." As a matter of fact, I do think about his life in the United States and I sometimes compare myself to him. Life here has a lot of ups and downs, too. I wonder what will happen to me.

Father

Heyneker: My father, Louis Heyneker, was born in 1906 in Kansas City. The first nine years of his life he lived in the United States and his first language was English. He then moved back to the Netherlands with his parents during the First World War (Holland was neutral). He went to a Dutch school and had to adapt and learn the Dutch language. In those days, if you were not exactly the same as all the others, it was not so easy to blend in. People were not as open to new things as they are now and certainly not in the Netherlands. I understood from listening to my father that his initial adaptation was not that easy.

Hughes: Do you think he felt himself to be an American?

Heyneker: Well, perhaps in the beginning because his English was much better than any of the kids', and his Dutch was much worse than any of the kids'. So he had to conform. He turned out to be a very good tennis player. He enjoyed that sport a lot and was one of the top players in Holland, I would say one of the top five during his prime.

Hughes: So he played competitively?

Heyneker: Definitely. And he definitely was competitive.

He studied physics at the University of Utrecht. He graduated in 1932. In those days, it was a very difficult time to find jobs—serious depression. We're talking about the early thirties. So he ended up with an insurance company where he had to come up with all sorts of tables and tabulations to predict how old people would get and what the chances were for serious illnesses, et cetera, et cetera. It was disappointing for him that with his background and education there were not more opportunities. After the Second World War he made up for it. He definitely had some significant highlights. Perhaps it doesn't matter where you start; at one point in time you will find your niche.

My father met my mother, Catharina Wilhelmina Stroink, at a tennis tournament. My mom was six years younger than he was. She studied chemistry in the University of Leiden. It was sort of unusual in those days for women to study the exact sciences. When

they met at this tennis tournament, it was love at first sight. I think they got engaged six months later and stayed engaged for quite a while because it was very difficult to get married. Well, not difficult to get married, but there was not much money around.

Hughes: It was the Depression.

Heyneker: Yes. I think it turned out that the parents of my mother sponsored them for a while. They could not afford housing. They lived in Amsterdam. Everybody had to chip in to keep the show going.

Wartime Hardships

Heyneker: My older sister Toosje [Catharina Mauritsia] was born in May 1939, just before World War II. (I have a younger sister, Hanneke, who was born in 1947.) Germany invaded Holland in May of 1940. That definitely changed the life of my parents significantly. My father of course didn't want to go to Germany, so he lived a very sheltered life. At one point in time young able men had to go to the factories in Germany. The only way not to go was to go into hiding. It was not as severe as the way the Jewish people had to hide. It was not at that level, but still you had to keep a very low profile.

Hughes: Was he able to work while he was keeping a low profile?

Heyneker: I think in the earlier years he was able to work. It became grim in the last years of the war, 1944, 1945. Before that, he continued to work at the insurance company.

I was born in 1944, January 22. That was not the best timing because it was very difficult to get food, especially in the western part of Holland where the big cities are located, Amsterdam, The Hague, and Rotterdam. There was not enough food to go around. That was a problematic time. Luckily, my parents had a whole bunch of very good friends in the neighborhood, and when the times are hard you sometimes pull through because you become a very close-knit group. Listening to these stories was fascinating. Yes, it was very tough. At the same time, they had also in a way a lot of fun. They made the best of it, let me put it that way. They had very intense stories and intense friendships because it was a very difficult time.

After the war, my father became involved with the military. In the early days—1945, 1946—it was a priority to help get the nation back up. He was involved in rounding up and registering the people who were collaborating with the Germans during the war. There was a big group of Dutch people called the NSB. To a large extent because of the Depression of the thirties, a lot of people were looking for an alternative political system to get a better life. So Hitler's philosophy (National Socialism) had some appeal because of the difficult circumstances. The line was drawn for those people who continued to collaborate with the Germans after the Jewish people were being rounded up and deported. If you had not declared loyalty to your country at that stage, you were considered wrong. Then, after the war, you were prosecuted.

Hughes: So loyalty became a legal distinction in terms of being able to prosecute?

Heyneker: Yes, I think so. Our language is more closely related to German than it is to English. In the very early days of the war, there was probably a reasonably large group of people who were disenchanted with their way of life; they were ready for something else, and they felt attached to the German way of thinking. Holland was and is very tolerant of different people and different beliefs. When that trust was violated, that was not acceptable.

Father's Employment with the Dutch Ministry of Defense

Heyneker: After the first years of being involved with the military, just helping to get things going again, my father became an employee of the Ministry of Defense. Over time, he became involved in the counterintelligence area. He built quite a nice archive, or a method to gather intelligence, mainly from communist countries. Those were the days when you could not store information on computers. You had to do things by hand and by card systems. So he became an expert in technical intelligence, for instance, when it became known that there were big freight trains moving from Moscow to the south, and there were some other vague indications. By combining these indications, you can indirectly gather information that there's something going on. So he built quite a sharp picture of what was going on based often on publicly known information.

Hughes: He created this approach?

Heyneker: Well, he was not alone. There was a whole group of people involved with intelligence gathering. But he built himself this interesting niche and became well known for it. He had very good interactions with American colleagues, but also colleagues in Israel who wanted to use his technology to build on. It was quite exciting, as a matter of fact. He always knew a lot.

At the same time, I feel the information had an impact on him as well. For instance, he was absolutely convinced that it was just a matter of time before World War III would start, where communism and the free world would clash. He was convinced of that because he knew so much. In the days of the Cold War we were scared of these things. A lot of information was hidden from the public.

Father-Son Friendship

Hughes: How much of this sort of thing were you aware of as you were growing up?

Heyneker: Quite a bit. I talked a lot with my dad. I was his only son. I did a lot of things with my father. We went to Austria every summer to hike in the mountains for weeks on end. That gave me a good chance to talk to him, or he talked to me, perhaps.We talked a lot about politics. We played a lot of chess. He was a very good friend. Yes, I really think I knew him quite well. He was absorbed by his work, which was very intense and scary.

Hughes: Did you play tennis with your father?

Heyneker: No, I didn't. He stopped playing tennis from one day to the next. I asked this question many times, "Why have you stopped?" Because he was so good. He didn't like to play just for fun; he wanted to play competitively. When he couldn't play as competitively, he was no longer excited about it.

Hughes: There seems to be a theme among the generations of willingness to take risks.

Heyneker: I think my grandfather was more of a risk-taker than my dad. My dad was very loyal. He definitely would stick it out.

What else can I say? He had a very good marriage. I always had a good home to go to, which I'm very grateful for. He was always very encouraging of me.

Mother

Hughes: Maybe this is the time to talk about your mother.

Heyneker: My mother was born in 1912. She met my father in the tennis circuit when she was studying chemistry in Leiden, as I mentioned. My mother was a pretty good tennis player as well. She did finish her studies, but she didn't use it in a profession. She was a homemaker, took care of the kids. I think she never regretted that. That was her task. In those days it was much more the norm than it is now. I know much less about my mother, except to say that she was always there for us. When I came home from school, she was there to listen to my stories. Tea was always served. That sort of stuff. She was very helpful. But in the family, my dad was the more dominant person.

Hughes: And he was the one that you had deep conversations with?

Heyneker: Yes, much more than with my mother. Although I always loved her dearly. It's a little harder to say a lot of things about her. She led a more sheltered life. She followed my father. I don't think that she was as excited to go to the mountains as he was, but there was never a discussion that she wouldn't follow. She had a fear of heights. So often my father and I would go on a tour for a couple of days, staying in huts, and my mother would stay in a little village with my sister.

Maternal Grandparents##

Hughes: You haven't talked about your maternal grandparents.

Heyneker: Correct. I know much less about the parents of my mother. I did not know my grandfather from my mother's side. Only I know that he lived in the eastern part of Holland, and he had quite a successful import-export business in cotton, cotton which he got from the United States, okay? [laughing] Yet another link with the United States. He passed away in his early sixties, before I was born. Probably in the thirties.

I knew my grandmother from my mother's side, but I only knew her for probably eight years. I think she passed away in the early fifties. She was very rheumatic. She had difficulty moving around and about, but she was very, very gutsy. I think she was always in pain, but she was a very nice lady, very cheerful.

Hughes: How much a part of your life was she?

Heyneker: Well, not that much, unfortunately. She lived in the eastern part of Holland and we lived in the western part. In the first ten years after the war, we didn't have a car. We did visit her a few times per year during holidays. I often spent time during my summer vacation with her and with my uncle Herbert (after whom I was named) or aunt Riekje.

My older sister developed some form of tuberculosis after the war. She was quite sick for a long time. She was being treated by a professor in Amsterdam, apparently quite famous. He was Jewish, but he was so well known that the Germans did not deport him, but let him continue his practice during the war She had to recuperate for a long time, and she spent lots of time with my grandmother in the eastern part of Holland.

Hughes: It was too much for your parents to give her the care she needed?

Heyneker: Right. Also, there was much more food in the eastern part of Holland than in the western part.

II EDUCATION

Early Schooling

Hughes: Is the next step your education?

Heyneker: Sure. I was born in Amstelveen, which is a town which borders Amsterdam, so it's a sort of a twin city. We moved to The Hague when I was four. I grew up in The Hague.

Hughes: Was that because your father was now in the ministry?

Heyneker: Yes, exactly. The Hague is where the government is. Amsterdam is the capital of the Netherlands; it has mostly commercial activities. The Hague is where the parliament resides and the ministry. That's where I went to school. The system in Holland is a little different than here. In Holland, every class you have to pass to go to the next class. If you don't pass, you stay for another year. You don't know in advance what year you will graduate; it depends how you move through the school system. I didn't have a lot of trouble with school, luckily.

Hughes: What were your academic interests?

Heyneker: I definitely focused on the sciences.

Hughes: Why?

Heyneker: That's what I liked. I liked to solve puzzles. I liked to solve algebra problems. I was terrible at languages, and I still am. But I really always enjoyed learning about chemistry, physics, et cetera. It came naturally.

Hughes: More the physical sciences than biology?

Heyneker: Yes, probably, because in those days there was no molecular biology really; biology was all descriptive. It was a little vague.

Hughes: You preferred the more quantified?

Heyneker: Exactly.

Undergraduate, University of Leiden, 1961-1965

Choosing Leiden

Heyneker: I entered university when I was seventeen. I got a room in the town of Leiden where I studied. You start forming a club with your friends. It's all great, okay, but I think I had still a lot of growing up to do. To combine my new-found freedom with study was definitely not so easy. Also, my friends there were often older than I was because either it took them longer to get out of school or they went first to military service and then they started at the university. I felt that I was not as far developed as the other guys who were two, three, four years older. But I got a lot of support. Looking back, I think those were the best of times.

Hughes: Why the University of Leiden?

Heyneker: Several reasons—very pragmatic. It was close to The Hague, so for the weekends I could go back home if I wished. It has a good name. My mother went there, also studying chemistry.

Hughes: You made an application to Leiden and that was it?

Heyneker: Exactly. It's not like the States. You have the right to go to a university when you pass your final high school exam. So you only fill out the application if you want to go here, there, or the other place.

Hughes: Why chemistry? [pause] And did you have to make a decision right away about where you were going to focus?

Heyneker: Good question, because I often still say that I wish I would have studied medicine.

Hughes: Was that a consideration?

Heyneker: Yes.

Hughes: Why did you decide not to?

Heyneker: Because chemistry appealed to me as well. [pause] I was young; I didn't think it through. Look, I have no regrets, because I'm more than happy with where I ended up. But especially early on I missed the connection with medical school, the connection with the patient. But, listen, in life you have to make choices. And I have made a lot of choices in my life, some good, some bad, but that's the way it is. You can't be in two places at the same time.

A High School Mentor

Hughes: Tell me about the years when you were an undergraduate in chemistry.

Heyneker: At the end of roughly four years, we get our *candidaats* exam. It means that you have gotten your undergraduate degree. The way it works in Holland is that then you have to go through a program where you get your master's degree, a two- to three-year program. Only then can you move on to a Ph.D. program. What the master's program does for you is to get theory out of the way. So once you are in your Ph.D. program there's really only practice—do the experiments.

Hughes: During your undergraduate years, were there any people that influenced you, either on the faculty or off?

Heyneker: Let me go back to my high school years. I think the main reason why I decided to study chemistry was not my mother, but it was my teacher in high school. It was Dr. Zeeper. He was extremely funny, and he really could explain chemistry in a way that appealed to me. I know that there were a lot of people in the class that hated him because exactly what I liked in him they couldn't stand. It clicked and I really felt that chemistry was very intriguing. I understood it sufficiently to become excited about it.

Hughes: What was there about chemistry that excited you?

Heyneker: How it works—breaking things down to the small building blocks. Everything around you is chemistry. Even in biology, good old chemistry rules apply to these complex matters. So I found it very intriguing and exciting how it's all organized.

Hughes: Was this organic and inorganic chemistry?

Heyneker: Both, yes.

Focus on Biochemistry

Hughes: Were you getting any exposure to biochemistry?

Heyneker: In high school there was zero biochemistry. But when I started my program at the University of Leiden in 1961, it was the first year that biochemistry was introduced as a direction in undergraduate schooling. That's as close as you could get to the medical faculty. As a matter of fact, there were some professors from the medical faculty who were teaching in this program.

Thinking back to my undergraduate schooling, I was motivated by completely different things than science. I was motivated by having fun, by sleeping in, by doing all the things you do when you are in undergraduate school. I did the bare-bones minimum to get by. I was way behind. But then one day I decided, "Come on. I have to get my act together." So

I did a few of those exams, and I think I got my undergraduate degree probably a year late.

Hughes: Was there anybody in the undergraduate period that you had a particular relationship with?

Heyneker: [pause] Not really. You know, I was probably just young. I had different motivations. I was not really thrilled by science at that time. It's mainly that I wanted to get a degree, and then the world would open up again. I was naive.

Master's Program in Biochemistry, 1966-1968

Hughes: Were you always going to go on to a higher degree?

Heyneker: Definitely go on to my master's degree.

Hughes: Why were you so definite?

Heyneker: Because people don't stop at this *candidaats* level. If you start studying, you normally go on to your master's degree.

Hughes: Was it more or less a given that if you started at Leiden, you would keep on at Leiden?

Heyneker: Yes. Later in life, when I advised people in Holland, I made pleas to say, "Look, broaden your view. After your undergraduate studies, go somewhere else to meet with another group of people." I found it very refreshing when I came here that you are encouraged to hop from one place to the next.

Can I offer you a glass of Chardonnay?

Hughes: I think I won't, but I encourage you to have one.

Heyneker: [laughs] To loosen up.

Hughes: [laughs] You're plenty loose. I get migraines from alcohol. What about the story of the next two years for the master's degree?

Heyneker: Officially it is around three and a half years.

Hughes: That long? So it was really quite a program.

Heyneker: Yes, although I don't think that we were working that hard at the university. I think we work harder in high school, and probably once you're in your Ph.D. program you start working pretty hard again. In my days, university was—I can't say that I overworked myself. It was the good life. The sixties were good. We were convinced that we would find a job at the end. It was definitely the years of innocence.

Hughes: Were you politically involved at all?

Heyneker: No. There was not that much politics going on. I couldn't associate myself with the left-wing movements. I didn't agree with them. There was not that much right wing going on. I felt that I was democratic. Over time, I think I have become more left wing.

Hughes: How were you engaging with chemistry in this master's program?

Heyneker: Well, not very well. It never occurred to me to drop out—no, that was not an option—or to change my studies, let's say to medicine. I was on this track, okay, and I will finish it.

Hughes: How much of this lack of engagement, if that's the way to characterize it, do you think was because you were using this time to grow up? And how much of it was the way the curriculum was designed?

Heyneker: I think a combination of both. Although, if you really want to take advantage of university life there is so much to do. Listen, it's not that grim: At one point in time, I promise you, I did connect with the science; I did become engaged.

Hughes: [laughing] I'm not thinking of it as grim, and I know it's got to happen at some point.

Heyneker: I will tell you when, but not when I did research for my master's degree, not at all. I did my major subject in a neurobiology lab. I had to smash rats against a rim to break their necks so that I could snip off their heads, in order to measure GABA levels in different brain compartments.

Hughes: So you were doing biochemistry?

Heyneker: Yes, it was definitely biochemistry.

Hughes: Was it a deliberate choice to go in that direction?

Heyneker: I absolutely always wanted to do chemistry which had to do with medicine. That I knew intuitively. But the quality of the research in neurobiology I could not get really excited about. I was floundering again.

Then I met up with two good friends who were more studious types, more like nerds. One was Pieter Molenaar, the other one was Rof Aalbersen. Those guys were really motivated. So I said, "Look guys, you have to take me under your wing because I want to get going here." So they did, and I must say it helped. That's probably the best thing I did. All of a sudden I said, "Okay, I'm going to get this degree."

Hughes: They motivated you to get your project done?

Heyneker: Right. It was, "Look, I'm not going to hang around here for years and years because there's more to do in the world." I wanted to get out of there. So I did my master's degree in two and a half years. It was quick, and I must say I got better work habits. But to ask was I motivated, and were there people who really influenced me in those days? The answer is no. There were some people in the lab who I couldn't stand. It was not my cup of tea.

Hughes: Was the professor a distant figure?

Heyneker: A little. He was an okay guy, by the way. I wanted to go into clinical medicine where you start running a lab where you analyze samples, do clinical tests. Again, trying to be close to patients.

Hughes: He wasn't interested?

Heyneker: He was interested, yes, but I had to go on military service first.

Military Service at TNO, 1968-1970[1]

Military Training and a Project on Nerve Gas

Heyneker: Military service in those days was mandatory. You could either do it before your studies or after your studies. After my master's, I enrolled. That was the turning point. My father got me into an accelerated program in which you become an army officer in the army after a short course of a couple of months.

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Heyneker: I was working in the laboratory of the Research Defense Organization—basically chemical warfare, biological warfare, whatever. All the things which are of interest all of a sudden yet again. I started working on nerve gas.

Hughes: Because of your background in chemistry?

Heyneker: Right. I started to work with a professional there, sort of as his student or technician. But the good news was that I became quite enthusiastic about it. The quality of the research was very good and was well thought through. It was very civilized research. It was very defensive research. We were aware that these nasty chemicals were out there. It was very basic research, trying to understand in detail.

Hughes: This was the early sixties?

Heyneker: No, this was late sixties. I entered university in '61, and I finished in '68, and then in '68 I went into the military service.

Hughes: For how long?

Heyneker: Two years.

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1. *Toegepast Natuurwetenschappelijk Onderzoek.* Rough translation: Applied Research for Life Sciences.

A Dissertation Project in Genetics

Heyneker: So after a quick stint, running through the bushes and so on and getting my training, I was then sent to this laboratory. That's where I started to get really my enthusiasm. I did this chemical stuff for a half of a year, and then I was transplanted to a more biology-genetics project.

Hughes: Did you ask for the transfer?

Heyneker: Yes, I did.

This institute was closely associated with the university, so it was sort of a postdoctoral institute. There were a lot of highly specialized people there.

Hughes: But under the military.

Heyneker: Yes, it was organized under the Ministry of Defense. But there were clear links with the university. I wanted to start on a Ph.D. program, to get started on a thesis.

Hughes: Was it a new idea to go on for a Ph.D.?

Heyneker: Well, yes—all of a sudden. You definitely guide me here. My original plan was to go into commerce or into this clinical laboratory. But once I was at this institute and I saw how carefully experiments were being conducted and how interesting those experiments were, all of a sudden a spark flew over, and I really wanted to do well-controlled experiments. I got it. I got it. So I decided, "Perhaps I should do a Ph.D. program." I talked to a guy who really influenced my life, Dr. Pieter Pouwels. He was the head of the department of genetics.

Hughes: Was Pouwels a career scientist at the Department of Defense?

Heyneker: Yes, although perhaps we should define it slightly differently. Yes, it was run by defense, but it was quite independent. It was not a top-secret institute with barbed wire around it. Not at all. I think it was comparable with SRI [Stanford Research Institute]. That's probably the best comparison. Because SRI does a lot of military research as well.

Hughes: Would an academic scientist respect the institute?

Heyneker: Well, right, unless you don't agree with the type of work we were doing. I think it was the top institute in the Netherlands. TNO still has a good name. A lot of the career scientists there have university positions as professors. The good news is all of a sudden I became exposed to those top-quality people. For instance, Pieter Pouwels did a postdoc for three years at Stanford with Paul Berg. So there was a very good connection. The level of science was very similar to what was going on here.

Hughes: How would Pouwels have defined himself?

Heyneker: As a molecular geneticist. Molecular genetics is really a good way to describe it. We were already working on DNA very early on. That will play a big role for the future, so let me not go ahead of myself.

Research on DNA Repair Mechanisms

Heyneker: So I decided to work with Pieter Pouwels on a subject entitled, "The Repair of DNA Damaged by Ultraviolet Light." When DNA is irradiated with UV light and other high-energy sources, it becomes damaged, not just in vitro—in a test tube—but also when you are exposed to UV in the environment. Cells have a mechanism to repair the damage. If not, your genetic information would become useless in quick order.

I started on the project. I tell you, I became more and more enthusiastic by the day. All of a sudden, I spent long days and weekends at the lab, and I loved it. Very much like what you expect once you are truly in graduate school. Finally, I became engaged. It was fantastic. Great people there. I learned a ton. When I talked to Pieter Pouwels in the beginning, asking him if I could work for him, I was still incredibly naive. I had no idea what I was getting into. But he was a super guy and patient, and I must say, I think in the end I redeemed myself.

Hughes: Do you think that he saw your potential?

Heyneker: I hope so. He could use me. I think if I would not have worked out he would have kicked me out, and rightly so. But it turned out that I am good with my hands.

Hughes: Were you just discovering that?

Heyneker: Yes, probably. I'm very disorganized, but my experiments are pretty good; they are organized. I learned to use all the right controls, to make sure that you learned always something from an experiment.

Hughes: Even when it failed?

Heyneker: Exactly, because a failed experiment failed for a reason. You have to understand why it has failed.

Hughes: Was this the kind of thing that you were learning during this experience?

Heyneker: Absolutely. Pouwels was a very good teacher, but I understood it intuitively. Perhaps I was lazy; I hated to repeat a lot of experiments. I'd much rather do it right the first time. When you see the results and it works, it's fantastic. I really got very enthusiastic, and work went extremely well.

Hughes: Tell me in a little more detail about your research on DNA repair.

Heyneker: We were definitely playing with DNA—that was 1971 to 1975—in a quite sophisticated way. We chose as a model system the circular DNA of a bacteriophage, which is a

bacterial virus. This particular bacteriophage, PhiX174, was studied all over the world. The virus particle contained single-stranded circular DNA. When that bacteriophage infects an *E. coli* cell, it injects the DNA into the cytoplasm. There, the DNA is replicated into double-stranded DNA. By grinding up the bacteria, you can separate that circular DNA from all the rest of the *E. coli* DNA. So you had something which you could purify.

The beauty was, this DNA had biological activity. If you had secured DNA, and you would bring it together with bacteria under the right circumstances, you could introduce that DNA into bacteria. Since the DNA had all the functions for bacteriophage, you would get the phage out of it. So the DNA maintained its biological activity. That's very valuable because if, for instance, you irradiate that DNA, your biological activity drops.

Hughes: Right, because it's damaged.

Heyneker: Because it's damaged. But on the other hand, bacteria like *E. coli* have also repair mechanisms. When you put the DNA back in the wild type *E. coli* strain, most of the damage would be undone, and you will still have maintained quite a bit of biological activity. However, there are a lot of mutant strains where this repair mechanism is affected in many different locations. It's a very complex process. There are several different mechanisms which run in parallel in bacteria to repair genetic material. When you introduce DNA into those mutants, all of a sudden you'd see an enormous drop in the biological activity upon irradiation. There was a huge difference between the wild type and mutant strains.

Hughes: Did your group discover this?

Heyneker: No. That's a good point. When I came there, that was sort of known. Certain things were known better than others, but the principles were known, yes. That's definitely the backdrop. People were used to studying this PhiX174, and there were methods already worked out.

Hughes: PhiX174 was the model organism?

Heyneker: A model organism. Well, one reason why people were using it was because the DNA's infectious. And two, it's a very small loop of DNA. It's only 7,000 base pairs in length. So it is nice to play with. Nothing was known about it: no sequence data, no restriction enzymes, no nothing. That was all pre-recombinant DNA technology.

So here was my task, and that's what I did in the four years I was there. This is the summary: I demonstrated that when you irradiate this double-stranded form of this phage, I could repair this damage in vitro. I isolated the enzymes which were involved in that repair process. It was a UV-specific endonuclease, an enzyme which recognized the pyrimidine dimers. The pyrimidine dimer is basically the site of the damage. If you don't repair it, that DNA becomes biologically inactive, so you need to repair it. Therefore, *E. coli* came up with mechanisms to repair it.

One of the enzymes was this UV-specific endonuclease, which recognizes that position and cuts next to it. In the strand where the dimer was there was a nick next to it. The second enzyme, DNA polymerase, recognizes that nick, sits there, and it does two things: it starts incorporating new nucleotides there, and at the same time, in front of it, starts

tossing out the other nucleotides, including the dimer. So the nick, the break in the DNA, starts here and the dimer is next to it. The nick gets translated. Then the last enzyme is a ligase which repairs that nick. So you're back with a double-stranded DNA, but the pyrimidine dimer has been removed. And also biological activity is restored, because we have this bacterial strain being used which is very sensitive to this because it has the mutant in it. This strain could not repair DNA. So when you give the DNA to that strain, your biological activity drops very rapidly. Once you carry out this repair process in vitro, you demonstrate that biological activity is restored.

Hughes: Where is the novelty in what you were discovering?

Heyneker: Well, we were the first to demonstrate that these enzymes were sufficient to carry out this repair process.

Hughes: You're using "we" in the royal sense. It was really Herb Heyneker?

Heyneker: No. First of all, you never do things in isolation. So "we" was meant as the group, Peter Pouwels and others. You always discuss your work with other people.

Hughes: But you were the hands?

Heyneker: Yes.

A Basis for Research on DNA Repair in Higher Organisms

Hughes: Give me a little context.

Heyneker: It was a very interesting piece of work that we, this repair group, were doing because it opened up some doors to find other interesting things. It opened the door to find comparable mechanisms in higher organisms, in eukaryotic cells, instead of bacteria. The understanding we have now of DNA repair mechanisms in human cells is very significant; it's very complex. But there are a lot of similarities with the simplistic system in bacteria. So the work served as a starting point for more sophisticated and elegant studies. There is such strong correlation between repair of DNA, or lack thereof, and cancer, or DNA which is repaired wrongly or not repaired.

Hughes: Were those ideas in the back of all your minds at this time?

Heyneker: Well, it was in the back of the minds probably of the people at the Ministry of Defense. It was more like, "Gee, how can we protect against radiation? What is the underlying mechanism and what can we do about it if we are being exposed to, let's say, an atomic weapon, or whatever." This is not UV radiation, but another type of radiation.

But there are mutants—and that was known already in those days—in humans where people are exquisitely sensitive to UV radiation. Scleroderma pigmentosa patients come to mind as a group of patients who are deficient in a certain repair mechanism.

Hughes: But you, Herb Heyneker, were doing a basic science piece of work. Somebody in the ministry maybe saw the relevance to practical problems, but that wasn't foremost in your mind.

Heyneker: We wanted to understand it. What I described now took place in 1973, 1974. There was no commercial opportunity. We did this because it was interesting science, and hopefully we could learn something from it which could be helpful at one point in time.

Hughes: Were you exchanging data with groups in other institutions?

Heyneker: Absolutely.

Competition and Motivation in Science

Hughes: Was this a competitive or collegial situation with other groups?

Heyneker: I would say "Yes," and "Yes." Yes, the field was always made up of competitors, but they were often friendly competitors, right? So you do it together, but you try to be the first. [laughter] That aspect I liked a lot. I definitely wanted to be first; I was definitely competitive.

Hughes: Had you known that about yourself?

Heyneker: I see it as a race, or like playing racquetball or whatever. Lots of scientists have that competitiveness, and you need it. You have to be driven by it. If you only do science between 9:00 and 5:00, you perhaps might want to do something else. Scientists are not working hard because they have to; they are working hard because they want to, because it's fun. I think being in the forefront, and discovering new things, or being first, goes hand in hand almost. It's very exciting, and I think it's very critical for a scientist to have that enjoyment. It's like mountaineering. Why go through all this agony to go to the peak? Well, you have a nice view, okay? But thereafter you can walk for a long time in a deep valley before you scale the next peak. Why do you do this? Because you always want to scale the next peak, look at the landscape from a new perspective.

Hughes: And your colleagues will notice that you've scaled a peak.

Heyneker: Yes, sure. That's a big issue by itself. The rewards you get in academia are recognition to a large extent. The people in academia who are successful get significant recognition for their work, much more so than in industry, I would say. In industry there are other ways to reward people, for instance, financially.

Hughes: Does money motivate a scientist?

Heyneker: Sure. It's also a form of recognition, in a way. Both extremes are less desirable, but the extreme in academe that people get their jollies out of recognition is a little dangerous sometimes, I would say.

Hughes: Expand on that a bit.

Heyneker: It might get a little in the way of collaborating. It can become vicious now and then. That's not necessary, I feel. The problem often is that there are no other forms of recognition in academia. It's now a bit better, but people in academia used to behave quite poorly. Look, this is a little bit of philosophy, and all in all people in science are in general very pleasant and nice to deal with. I was just touching on some of the extremes.

Doing Science as a Team

Hughes: Would you go so far as saying that because in industry there's the potential for rewards aside from peer recognition that a more collaborative scientific approach is more likely?

Heyneker: Yes. For instance, at Genentech—

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Heyneker: —there was a paper with something like twelve or fifteen authors on it. It's becoming quite normal now.

Hughes: Yes, but not then.

Heyneker: But not in 1982, or whenever. We got a lot of comments: "Why so many names on it? Not everybody did it." I said, "Wait a minute. There's a reason we put all these names on it. Everybody contributed and collaborated. Therefore, we were able to be first, and not because somebody is doing it all by himself in a lab to try to get the recognition." I think it is very rewarding to be part of the team. I like it because you discuss your project with many different people, so you get very good feedback. It helps you direct the research. I think it's a very efficient way of doing things.

Hughes: I can imagine that the science itself dictates whether the logical approach is through a collaborative group effort, or through an individual scientist sitting in his study and thinking it through.

Heyneker: I think it has to be a combination of the two. You don't get there just by forming a big group. Perhaps these days you can. Some of the current scientists don't have to be very imaginative; it's just a lot of hard work. But let's say it is imaginative science. To have a big group is not enough; you definitely need some creative people there. I always say that one brilliant guy is worth more than ten very good people. You need that spark of somebody who can think outside of the box and move you over a hump—somebody who comes with a new technology or new approach to do something. Yes, you need that. But that's often not enough. You need the combination of creative leadership with the manpower to carry it out. Genentech was extremely good at that in the early days.

Doing Science Outside the Box

Hughes: Since we have jumped ahead of ourselves to Genentech, would it be accurate to characterize your role as that of a catalyst in some of the early projects at Genentech?

Heyneker: Yes, I think so, but not because I feel I'm brilliant. We were also at the right place at the right time. We were picking the low-hanging fruit. For the outside world, we were probably very good, but for the inside world, for the rest of the people who were doing this work, we were plodding along, just like everybody else.

Hughes: I have gotten from talking to people, specifically Dave Goeddel, about the early period at Genentech that you were able to come in and make experiments move faster and more efficiently.

Heyneker: That's very nice of Dave to say. Dave and I worked well together. I had a little more experience than he in the early days, although later he ran way past me. I think we formed a very good team. Perhaps my strength is that I think outside the box. I must say, I love that. It's not always easy because thinking outside the box in your life doesn't always make your life easy. It's very exciting. That makes me come back to science—to do something, and lo and behold it works. That is fantastic.

I think a good example of this was in the early days at TNO, doing my Ph.D. thesis. There was an *E. coli* mutant which was impaired in this repair mechanism. We had an indication that the reason why this *E. coli* was sensitive to ultraviolet radiation was that there was an enzyme affected. We knew from genetic mapping that the region where it mapped was in the vicinity of DNA polymerase. I mentioned to my boss, Pieter Pouwels, "Look, I would like to test this hypothesis." Pieter Pouwels said, "Come on, don't do this. This is so crude. The chance that it is right there is next to nil. This is a total waste of time." So I did it in secret. And the result I got was so smashing, it was such a yes/no answer. I still remember when I saw the data I could not believe my eyes. It was BAM! It stood out completely.

I went back to Pouwels with the data, and I said, "Perhaps I should not have done this, but–." He said, "No, you should not have done it, but I'm very happy you did." So it was really great. The best part of this work is that we found this mutant DNA polymerase I, really proving, as I mentioned, that the polymerase starts out of nucleotides. It was a beautiful genotype/phenotype experiment, probably one of the first experiments of that type. People still, as of today, always like to find the correlation between the genotype and the phenotype. This was done in the early seventies. We beat Bob Lehman to the punch at Stanford who did something similar a year later.

I'm trying to tie this together. Perhaps I was not thinking outside the box, but I was doing things outside the box. [laughter]

I tell you, those are experiments which make you come back to the bench. Those are experiments which make you feel on top of the mountain. It is so—much—fun! My goodness, it is so much fun. That's what hooks you to science. I bet you that if I would not have had those experiences I would have ended up somewhere else. I might have ended up in clinical chemistry, why not? But because I was exposed to that sort of stuff, I

said, "Hey look, we devised this experiment the right way; we got this clear answer. We know why. This is a good base."

Mentors

[Interview 2: April 2, 2002]##

Hughes: Picking up the thread of your life in the Netherlands, I wonder if you have comments to make about influential people in your life—perhaps mentors.

Heyneker: Yes. As I mentioned, it took me a while to get enthusiastic about science. I was a late bloomer. There were several people who influenced me and gave me the spirits to do science and really enjoy science. The first person that comes to mind is a [promotion] mentor, Pieter Pouwels. I became quite influenced by him because of his rigorous approach to science, his understanding of the theory behind it, but also his excellent practical, technical, at-the-bench approach—how to carry out experiments. That helped me enormously. That game me the first hint or help to design experiments well. Whatever you do, you should [get] an answer. Nobody knows what the answer is, but you should not have to do an experiment over because you designed it wrong. Garbage in, garbage out, okay? The sooner you learn that, one, the more efficient you are in science, and secondly the more enjoyable it probably is.

Hughes: A negative answer would be acceptable as well?

Heyneker: Oh, absolutely. A negative answer is still an answer. What is not acceptable but of course in reality happens is that you do a wasted experiment. You cannot make any conclusions from it because the design was not good. Perhaps I am lazy, and I don't want to waste time, so to do efficient experiments is something I really enjoy. I did my promotion [to the Ph.D. degree] in 1975, so around thirty years ago I really got the fire to do this type of work. One of the reasons why I enjoyed it so much was indeed to get answers.

Hughes: Because you believe experimental design is key, do you spend a period of time thinking and plotting and designing before you start to do any bench work?

Heyneker: Exactly. Yes, that's the logical conclusion: don't go to the bench without having a plan. Unfortunately, I'm not the type of guy who planned it all out nicely in a notebook; I've often planned it out on paper towels. So I'm very scatter-brained. But when it comes to experiments to carry it out, I want to make sure that they work.

Hughes: In the Netherlands your experiments were exclusively done by yourself?

Heyneker: Well, that's a good point. I started out by myself, but the last two years of my graduate studies to get my Ph.D., I had the help of a technician. That's sort of unheard of in the United States as a graduate student—you do it all youself. But in Holland, you have a job, and you're being paid for it. It's comparable to an assistant professor job. In the early seventies when I did my graduate work, the economic situation in Holland was quite

favorable and there was enough money for research. That's why these excesses—that we had help—were the norm.

Pieter Pouwels comes to mind as really influential for me. Another person I would like to mention is my promoter, Arthur Rorsch. He was a professor at the University of Leiden. I mentioned that my graduate work was done partly at the TNO and partly at the University of Leiden. It was sort of a liaison between the two institutes. So that's why I could get my promotion at the university, although most of the time I worked at an institute which was not directly part of the university.

Hughes: How much attention were these two men paying specifically to you?

Heyneker: Arthur Rorsch was the head at a big lab. Whenever I had a problem or wanted to discuss something with him he was open, but it was not that he came to me to ask questions. Pieter Pouwels in the beginning was much more a mentor who on a day-to-day basis interacted with me till he probably determined that I could do things reasonably well on my own. I'd also like to mention a colleague of mine, somebody who did at the same time a promotion, and his name was Hans Pannekoek. He is currently professor at the University of Amsterdam and I still keep in touch with him. We helped each other quite a bit because he was studying a similar subject, and we talked to each other. I could go on mentiong quite a few other people—that's not, I think, the idea—but it was a great time and all of a sudden I felt it was a great job to have. Finding a position in research was very appealing all of the sudden.

Hughes: With the virtue of hindsight, how was this experience preparing you for what lay ahead?

Heyneker: It gave me very good preparation for what lay ahead. I was very much involved with work with DNA and enzymes which were involved in the DNA repair process. Later, when I started my postdoctoral work, enzymes involved with DNA, like restriction enzymes, were a very important enzymatic tool to put different pieces of DNA together.

Attending a 1973 Lecture in Ghent by Herbert Boyer

Heyneker: I'm ahead of myself because I should mention that what really changed my life was the fact that I went during my graduate studies to a lecture in Belgium, in Ghent. It was 1973, and Herb Boyer gave a lecture on the work he was doing in his lab, especially on the early stages of recombinant DNA technology.

Hughes: The experiments with Stanley Cohen had been done?

Heyneker: Yes, they had been done, but just very recently.

Hughes: Their first paper was published in November 1973.

Heyneker: Exactly. He was talking about these very exciting things: Combining pieces of genetic information from different species was unheard of. That was against every dogma. When

I heard his talk I became very enthusiastic. I understood it because he was working very close to what I was doing in a way.

Hughes: Was his a familiar name?

Heyneker: His name was already familiar, yes.

When I knew that Herb was working at UCSF in San Francisco I on the spot decided to approach him and ask him if I could do a postdoctoral fellowship at this place, knowing that I still had to do at least one and a half years of work before I would graduate. I wanted to do it for several reasons. I was intrigued by his work, but also San Francisco had this magical feel to it. If I wanted to be in the United States I would love to be here on the West Coast. So I mentioned to him that I would bring my own money if I would come for a postdoc, because I knew that in Holland, it was not hard to get a stipend for travel for a year. And his answer was almost immediate—he said, "Sure, come."

Hughes: Well, you had all the advantages: You had the money and you had the experience in a similar research area. [laughter]

Heyneker: Well, what turned out to be very helpful was that I did bring my own money. Only when I came to his lab did I realize that the system here in the United States was quite different. It was much harder for Herb to find the money for me, so the fact that I would bring my own money made life very simple for him; he could save the money from grants for other students.

Hughes: And do I understand you to say that you came to that decision at the moment of his talk in Ghent?

Heyneker: I would say yes. It was an impulsive decision to approach him and to ask him about the possibilities to join his lab as a postdoc, absolutely. So once he gave me his answer, I was euphoric. I said, "My God, this is incredible!" What an answer I got! I couldn't believe it! We started to correspond.

Attending a Conference in California in 1974

Heyneker: I came to one of the UCLA conferences in 1974—one of those conferences in Squaw Valley. Those were small conferences, very specialized, very nice, really great conferences. I gave a talk there or a poster—I think I gave a talk. I felt so privileged to be there and part of this whole beginning movement.

Hughes: What was the theme of the conference?

Heyneker: I think it was recombinant DNA. It was before the Asilomar conference, which was a year later, in 1975.

Hughes: February of '75.

Heyneker: There was already quite a bit of work going on. Once the cat was out of the bag that you could combine different pieces of DNA and reintroduce them in [a foreign] species, it opened up an enormous amount of possibilities, including possibilities which were considered dangerous. Hence the Asilomar conference. But in 1974 it was still a small conference attended by all the big names at that time in the field of recombinant DNA technology.

Hughes: Give me some of those names.

Heyneker: Stan Cohen, Paul Berg, Stan Falkow—

Hughes: David Hogness?

Heyneker: I bet you that Hogness was there. Dale Kaiser, Bob Lehman.

Hughes: Very Stanford, eh?

Heyneker: Yes. Mary Betlach, who was Herb Boyer's technician, was a very, very smart lady. Pat[ricia] Greene.

Hughes: Howard Goodman?

Heyneker: Yes, Howard Goodman of course was there.

Hughes: What about William Rutter? I've heard he didn't jump on the recombinant DNA bandwagon quite as early as others.

Heyneker: I think you are probably right. I can't recall that he was [at those conferences].

Hughes: Was one of your side motives for attending the conference to get to know this group that you would be associated with?

Heyneker: No, I was just delighted that I could be there. I don't think I looked that far ahead. I was not really planning a career, I was just delighted to be there.

Recombinant DNA in 1974: Scant Discussion of Practical Application

Hughes: Was the conference focused on basic science?

Heyneker: There were no principal applications yet.

Hughes: And no discussion of potential applications that you remember?

Heyneker: I can't recall any occurring in 1974. Art Riggs probably or possibly already had some of these ideas. I'll come back to Art Riggs later. I think he's an underappreciated, very forward-thinking scientist.

Hughes: What about Boyer? Do you recall him beginning to think about practical applications of recombinant DNA?

Heyneker: I don't know. If he did, definitely not in 1974, at least he did not share it with me at the time. The science per se was already interesting enough that you could dissect very complex pieces of DNA into much smaller pieces for studying. I'm jumping ahead of myself. My first project in Herb Boyer's lab was to clone a piece of synthetic DNA called lac operator. You dissect the lac operator from a much more complex genome, namely the *E. coli* genome, in order to study it in isolation. So those truly scientific questions you could all of a sudden answer, and that was exciting enough, really. When the more practical applications were envisioned, I always see it as icing on the cake. So I never went to Herb Boyer's lab with the idea that I would do some practical science.

Finishing the Thesis on DNA Repair

Heyneker: Anyway, once I had my postdoc lined up, that was a very good stimulant to finish my thesis in the last two years of my graduate studies, which I eventually did, in late October 1975.

Hughes: What was the title?

Heyneker: The title was, "Enzymes Involved in the Repair of DNA Damaged by Ultraviolet Light."

Hughes: Did it create interest?

Heyneker: I think so. It was a collection of four publications. The first publication was in the *PNAS* demonstrating that you could restore biological activity to DNA damaged by UV radiation.[2] Then there was a paper in which we did a structure-function analysis of this mutant DNA polymerase. The articles were published in decent journals, and so I got a bit of mileage out of them.

Hughes: That's a large number of papers for a dissertation, is it not?

Heyneker: Yes, but it took me a long time. I think I started in '69, and I finished my thesis in '75. So it took me at least six years, which is on the long side. But at the same time, I was not in a hurry—I liked the work; I was paid well; my life was pretty good. I had a technician; I had a very nice modern building where I had an office with windows and a wonderful lab where we could do all the experiments. There was way more money available for this type of work than in the United States. When I went to Herb Boyer's it was an incredible shocker, and I will come to that because it's so funny.

Hughes: Why was the money easy to get in Holland at that time?

Heyneker: Because Holland felt it was very important to do research.

2. Please see paper #2 listed in Heyneker's bibliography in an appendix to this volume. For the subsequent reference, see #3.

Hughes: So the government funded basic research in general. It wasn't that it was foresighted and saw that DNA repair was an important field.

Heyneker: No, it was not foresight; it was that Holland decided to fund science generously. Over the last five years, America is funding science generously also. So those things come in waves, and I promise you that Holland had to tighten its belt and became much less luxurious for a long time.

Hughes: So you were in the right place at the right time.

Heyneker: Yes, I think that's a phrase I will probably mention a few more times. I definitely was quite lucky.

Family Life

Hughes: Say something about your private life. Did you have a family?

Heyneker: I married Pauline Van Ijzendoorn in 1972 when I was twenty-eight. We lived in an apartment in an old farmhouse on the outskirts of The Hague in a town called Wassenaar, which was probably ten miles from Leiden Unviersity and probably fifteen miles from TNO. So I could easily go to the one place or to the other place. We started a family, and we stayed at the farmhouse till we went to the United States. [tape break] Looking back, those years were really carefree, upbeat, simple life, but quite nice. My major worry was to put my thesis together and get ready for the big step to do a postdoc at Herb Boyer's lab.

Hughes: How did your wife feel about coming to the United States?

Heyneker: I think she was very excited about it. We went to the United States with the idea that we would come back after one year, because I only got a one-year stipend. That's what the norm was in Holland, but things didn't work out that way; things changed.

Life in the farmhouse was nice. There was another apartment where two people from Canada lived, and they became very good friends. That's Frank Graham and Silvia Bacchetti. Frank Graham did some excellent work with van der Eb. Together they were probably the first to come up with a DNA transformation system for mammalian cells—the Graham-van der Eb method it turned out to be. The reason that I bring this up is that I had many, many great discussions with him about science over many, many games of chess, which he probably most of the time won, but it was an example of how private life and science melded together in a very nice way. I'm still in contact with Frank Graham and Sylvia Bacchetti. They worked at the TNO Institute so I knew them from there.

Hughes: Was it common to have foreigners there?

Heyneker: Yes, now and then. The TNO Institute had quite a good name, so it was definitely a place where people from other countries would come.

III POSTDOCTORAL FELLOW, UCSF, 1975-1977

Arrival in San Francisco

Heyneker: At that time we had two kids: Marc, who was three born in '72, and Thys, my middle son, was born in '75. He was half a year old when we went to the United States. Somewhere in the middle of November we arrived at San Francisco Airport and we didn't have a place to stay.

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Heyneker: [It had been arranged] for us to be in a guest house very close to UCSF, and that's where we went that day. All of a sudden we found ourselves in this guest house with some other people, mainly families of patients who were being treated at UCSF. It was on Forrest Street, walking distance to the lab. So here we were in a new country and it was all very different and strange and very exciting. I bought a station wagon for the family.

Hughes: [laughs] You were getting American very quickly.

Heyneker: Well, I had to! We found a place to stay, ten minutes walking from UCSF—a great place we rented. So I started to work there, and Pauline concentrated on the children.

Hughes: Did she feel isolated?

Heyneker: I don't think so. I would come back for lunch on a regular basis. It was very new for her too. There was enough to learn to keep her occupied.

Bringing Enzymes for Barter

Heyneker: I should not forget to mention that I arrived at the airport in San Francisco with a big bucket with ice in it. In the ice bucket were the enzymes I used for my DNA repair work. I had put in so much time to purify them, and they would otherwise be left in the freezer

somewhere. So I took them with me, not really knowing exactly what I wanted to do with them. Well, that turned out to be one of my better moves. They turned out to be very useful trading currency because one of the enzymes was DNA ligase. That was an enzyme that everyone needed to stitch DNA fragments together. In those days you could not buy your enzymes; you had to make them yourself. I have to say it was not my invention how to do it; I use a protocol I think from Khorana's lab.

Hughes: I take it that not many people—

Heyneker: Had that kind of knowledge. Right. So I had this ligase. I had also a tube full of polymerase. There was more than enough ligase to do whatever experiments we wanted to do. And the quality and the purity was good enough that this was desirable material.

Hughes: The Boyer lab did not have these enzymes?

Heyneker: If they had them, they were probably obtained from somebody else. They called up—basically doing science by telephone—to get a little bit here and a smidgen there.

Hughes: I think that the Stanford biochemistry group would probably have had those enzymes.

Heyneker: I think somebody had them, it was [Arthur] Kornberg and [Robert] Lehman. But to come by enzymes was not easy. You needed to know your source—where to get them. Often it meant a collaboration, and if you didn't want to collaborate, you had to make them yourself. I recall that over time I made a few more batches of ligase while I was at UCSF, and I made batches of polymerase because this was my knowledge. We also had to make our own restriction enzymes. Pat Greene, who was a postdoc in Herb Boyer's lab, came up with a very nice scheme to purify restriction enzymes. Almost everybody in Herb Boyer's lab had to learn how to do it. Different people in the lab were responsible for different enzymes, so we built a collection of restriction enzymes. The knowledge I had obtained during my graduate years, I could use immediately in my postdoc years. I think that gave me a flying start.

Postdocs in the Boyer and Goodman Laboratories

Heyneker: I must say those two years in Herb Boyer's lab were absolutely spectacular. We could not go wrong. We had so many wonderful experiments and successes, and there are several reasons for it. It was a great team. We were postdocs from several parts of the world. I want to mention Paco Bolivar from Mexico. I'd like to mention Axel Ullrich and Peter Seeburg, who did not work directly with Herb Boyer's lab, but they were in Howard Goodman's lab. And in the early days, Howard Goodman and Herb Boyer did everything together. It was basically one lab. Herb was on the fourth floor, and Howard Goodman was on the ninth floor.

Hughes: In the old Sciences Building?

Heyneker: Yes. I also want to mention John Shine, who was in Howard Goodman's lab. We all came as postdocs to the Boyer/Goodman lab with different expertise. I mentioned my expertise

was enzyme purification. Peter Seeburg had a very good knowledge about human growth hormone, and he knew already that he wanted to study that gene, and Axel Ullrich wanted to study the insulin gene. John Shine, from Australia, had already made a name for himself with a colleague of his, Delgarno. Together they came up with the Shine-Delgarno sequence, which was the promoter regions. We were all young. We all had one goal in life—to be as productive as possible as postdocs because that is your first step into the real world of science.

An Abandoned Initial Research Project and Research on the Lac Operator

Hughes: Had you come with a specific project in mind?

Heyneker: Well, I came with a project I wanted to do. I wanted to study a plant-transforming plasmid. There's a bacterium which induces crown gall tumors in plants. A big plasmid was responsible for this pathogenicity, and I wanted to study that plasmid. So that's what I did when I arrived. I dissected the plasmid, digested it into its different restriction enzymes to make a restriction map. We would sequence it now. But in those days sequencing was still very much in its infancy or nonexisting. So the best you could do was to make a restriction map of the plasmid. Now, I soon felt pretty lonely. Herb Boyer was very happy—whatever I wanted to do was fine with him. But I felt that I was not in the mainstream. So after a few weeks I said, look, this is ridiculous; this is not where I want to be. So I talked with Herb and said, "Look, I want to do something with you where I'm really involved with the lab." So, since I had all this experience with ligase and so on, he put me on a project that he and Art Riggs came up with that was to clone a piece of synthetic DNA which codes for the lac operator.

Hughes: Which was Riggs' interest?

Heyneker: It was definitely Riggs' interest, absolutely.

Hughes: Not particularly Herb's?

Heyneker: That's correct. But Art Riggs didn't have the tools to put the synthetic DNA in a plasmid and clone it.

Hughes: Because he only had synthetic DNA capacity?

Heyneker: Yes. He hired a postdoc away from Saran Narang out of Canada. And the guy was Keiichi Itakura, and he was very good with synthetic DNA. Art Riggs had the forward-thinking that synthetic DNA could be very important. He hired Keiichi and said, "Look, we're going to synthesize a piece of DNA which has some biological activity." They wanted to study the interaction of the lac operator with the lac repressor. It was for x-ray crystallography purposes. They wanted to have the structure of the lac repressor by itself and how it binds to this particular piece of DNA. So you could see how this interaction is very useful, very important. It was done in collaboration with a group from Caltech led by Norm Davidson. It was quite an important project. They needed milligrams of this lac operator DNA so that they had enough lac repressor to do these co-crystallization studies

and so on. Now we're talking 1975, 1976, and things were not so easy then, not as easy as they are now. We have learned a lot in the meantime.

Where Herb Boyer's lab came into the picture was that we wanted to clone the piece of synthetic DNA coding for the lac operator. Once you clone it, you can isolate enough plasmid and then cut the DNA out of the plasmid to have enough material to work with. So Boyer assigned me to the cloning project, and probably the main reason was that I had a lot of experience with enzymes which were involved in DNA repair—it was very similar.

Hughes: But you hadn't had experience with cloning per se, right?

Heyneker: Not with cloning per se, but the lac operator project was similar to DNA repair studies. It changed my life.

Scientific and Commercial Importance of Synthetic DNA

Heyneker: Ever since I have worked with synthetic DNA—at Genentech and most recently at Eos. The role of synthetic DNA in cloning and recombinant DNA technology in general is extremely important and has played an enormously valuable role in moving this cloning process forward.

Hughes: Well, expand on that a bit. How specifically is it important, and how specifically has it moved the field forward?

Heyneker: Well, it is very helpful to move pieces of DNA around but later became even more helpful to synthesize an entire gene instead of having to clone it.

The insulin cloning is an example where it accelerated the process because the competition which tried to obtain the DNA by cloning had a much harder time reaching their goal than we using synthetic DNA. But also synthetic DNA is very useful to bring certain elements, let's say a promoter element, in perfect alignment with a structural gene. Because restriction enzymes are not always at the position where you want them to be, you need to have some fill-in material to get the DNA segment exactly where it needs to be. Synthetic DNA was the perfect solution for that problem.

Hughes: Yet this was not a widely recognized technology.

Heyneker: Not in the early days. The fact that Genentech was the first to use synthetic DNA probably helped them to take the lead and stay in the lead for a long time. There's no question about it in my mind. We built up a lot of knowledge about how to make synthetic DNA, also how to use it in cloning processes, at a time that the rest of the scientific community was still struggling with that, or did not recognize the value as we did. It was a lead, which of course evaporated a few years later when people realized that DNA synthesis was important.

Hughes: In the beginning, the scientific advantages of having synthetic DNA capability at Genentech or anywhere gave those groups a leg up, so to speak. But was there also the added advantage that when the NIH guidelines came along they did not apply to synthetic DNA? Was that a factor at all?

Heyneker: [pause] No, I don't think so. It was convenient that we could hide behind that if we wished. For instance, when we later synthesized the gene coding for somatostatin, we were definitely aware that this could be biologically active material and potentially could have adverse effects. Although I would say in Herb Boyer's lab, we didn't believe so much that it was that dangerous. But still, it was not that we blatantly ignored the guidelines—not at all; I don't think so. Yes, we could always use the fact it was synthetic DNA, so natural DNA was not being transferred from one species to another. We could sort of hide behind it, but we never developed synthetic DNA capabilities to do so. To circumvent the guidelines was not the reason.

Hughes: It's quite clear in the way you presented it that it was on scientific grounds that you were using synthetic DNA.

Heyneker: Absolutely. A lot of this is hindsight. When you use synthetic DNA to help you with cloning processes you don't always see all the applications at that time. But looking back with all the applications we have now, you say, my goodness, synthetic DNA has played an enormously important role. Look at the current DNA chip technology—it's all synthetic DNA being laid down in little pieces which help us to sort thousands and thousands of different genes from each other.

Hughes: Genentech is known as the first company to be based exclusively on recombinant DNA technology, and yet what pushed Genentech ahead of the crowd is the combination of synthetic DNA capability and recombinant DNA technology. Yes?

Heyneker: Well, that's semantics to a certain extent. If you define recombinant DNA technology inclusive of synthetic DNA, it is still recombinant DNA technology. The alternative is to obtain your genetic information from cDNA [complementary DNA]. No, I would like to group synthetic DNA under the heading of recombinant DNA.

Hughes: So that statement is accurate.

Heyneker: Yes, your statement about Genentech being the first company [to be based on recombinant DNA] is accurate. But as a tool to accelerate and give recombinant DNA technology more flexibility, I would say synthetic DNA has been extremely helpful.

Hughes: And that is what Genentech had head and shoulders above any of the companies that were immediately to follow, is that true?

Heyneker: I think that's absolutely true.

Resistance to Practical Application of Recombinant DNA

Hughes: Now why was that? Genentech served as a model for other aspects of biotechnology.

Heyneker: Well, for several reasons. First of all, the molecular biology community was not ready for biotechnology or for practical applications.

Hughes: Why do you say that?

Heyneker: Because most people in science, especially in the biological sciences, were practicing science for science. As a matter of fact, when we gave presentations on the practical applicabilities using recombinant DNA technology, we were definitely looked at very critically.

Hughes: "We" at UCSF?

Heyneker: We in Boyer's lab at meetings—also at UCSF. Herb Boyer had a very difficult time to convince the pure academics that the practical application of recombinant DNA is valuable as well. So one of the reasons why synthetic DNA caught on slowly was that people were not eager to copy Genentech immediately. There was also quite a bit of skepticism that it would work. Only after we came out with a paper on somatostatin would people realize, wait a second, we can make foreign proteins in *E. coli*. It was a pretty landmark paper when it came out, and that might have been the start signal for other groups to look at more applied molecular biology.

Hughes: And they did?

Heyneker: And they did. But by that time, Genentech was off and running. We immediately did insulin, and, very soon thereafter, human growth hormone. So we were picking as quickly as possible the low-hanging fruit. And we were by far in the best position to go after interferon. And then it became harder. Urokinase and tPA—the bottlenecks there were to find the needle in the haystack, to find the gene coding for these proteins.

First Impressions of the Boyer Laboratory

Hughes: I've pulled you away from discussion of UCSF. [laughs]

Heyneker: But all those things are so intertwined.

Hughes: Well, step back and try to recreate your first impressions of the Boyer lab and the people in it and how Boyer interacted with you.

Heyneker: Yes, I'd love to do that. I still recall the first day: it was in the afternoon that I came to Boyer's lab. Although he knew I was coming, he had not prepared for it. His lab was very crowded. But that did not stop him from creating space for me, which he did in a very forceful way by pushing to the right a lot of the stuff of a future colleague, Ray

Rodriguez, and creating some space for me on the bench to the left, which included a sink. We put a little piece of hardboard over the sink, and my desk was a clipboard.

Hughes: What did you think about all this? You had had an office of your own in Holland.

Heyneker: I felt it was a step back. And I must say it was a little bit—yes. But people in the lab were very nice.

Hughes: Was everybody working in similarly crowded circumstances?

Heyneker: Yes. So that helped. I can recall the names of the people who worked in my particular lab. It was Paco Bolivar, and he had a girlfriend, Alejandra Covarrubias.

Hughes: Who worked there?

Heyneker: Yes, with him. And then there was Ray Rodriguez, whom I mentioned, and myself. And there was Russell—I forgot his last name. He was the guy who picked me up from the airport. So we were five in the lab. And the lab [space for my experiments] was probably seven by five. And then there was another lab, roughly the same size, which was occupied by Bob Tate, Rich Meagher, Pat Greene—that's it, I think.

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Heyneker: —and where Mary Betlach worked.

Hughes: Was Boyer a presence in the lab? At the bench?

Heyneker: Yes. He was at the bench now and then. He did some experiments. He was leading his group, probably writing some grants. Sort of fifty-fifty.

Hughes: Nineteen seventy-five—he had by then an appointment in biochemistry, didn't he?

Heyneker: He was still in microbiology.

Hughes: His appointment changed that year.

Heyneker: I think so, because he had a big fight with the people in microbiology.

Hughes: Are you thinking of Ernie Jawetz, the department chair?

Heyneker: Could well be. Anyway, it was a little bit unfortunate. The microbiology lab was run the way it probably was run over the last twenty years, and here comes Herb Boyer with all these new ideas. At least he built it to a vibrant place, for sure. And that might have caused some problems, I would say. Herb was probably not the most diplomatic type. Yes, he did join the biochemistry department while I was there. I don't know exactly when, but for the two years I was there, I stayed on the fourth floor [in mircobiology]. I did not move to the ninth floor [in biochemistry].

So my first impression was that, my goodness, this is a very crowded lab. Also, things had to be done very economically. We did have plasticware, like Eppendorf tubes and

pipette tips, but we washed them because there was not enough money in the beginning to throw them out and buy new. Well, in Holland I was used to you use it and throw it out the way it was meant to be.

So there were a few indications that you had to economize. But what I also learned was, that didn't matter; the lab had great results. It was fantastic. It was good interaction being close together in a lab; it is very helpful to go over each other's experiments. You can't help it—it's so close by you look at each other's experiments all the time, which was great.

I was quite close to Annie Chang who was Stan Cohen's technician. I met her at that Squaw Valley retreat in 1974. We spent time together, discussing things, and she helped me to look for houses. She helped me to get acquainted with the area. She invited me to Stanford to give a seminar. I gave a seminar on DNA repair and basically had a standing invitation from Stan Cohen to come to his lab. The labs were much nicer there. The weather was much better. Stanford University looked very inviting. Here was I in November in Herb Boyer's lab. It was cold, the fog was roaring around the corner, and I was tempted to say, "Let me go to Stanford." But I am happy that I didn't do it—very happy. Also I felt it would be such a betrayal. Let me first understand the workings before I make a desperate move. But I have to say it crossed my mind, because it was such an enormous step back. But once I got the hang of it, got to know the people—and they were super nice people; they were really wonderful—it grew on me. I loved it that we were close together. I loved it that we did things in an improvised way.

Hughes: Did you get the impression that most people in the lab were feeling the same way?

Heyneker: I cannot speak for the others, but I think, yes, because we had a lot of good times. It was definitely you work hard and you play hard. The lab came more and more together. When I came, people were doing their own thing, but by the time I left it was much more an integrated approach.

Hughes: Was the Boyer lab worse off than other labs in mircobiology?

Heyneker: I don't think so.

Comparison of American and Dutch Science

Heyneker: I got a taste how science was done in the United States in those days. And I must say that once I got over the shock, I was incredibly impressed with UCSF. I think the questions they were asking and the research that was going on were way ahead of anything I was used to in Holland.

Hughes: To what do you attribute that? Was it the mix of individuals that happened to be there at that time?

Heyneker: Also, I think it is very good that young professors like Herb Boyer have to write their own grants [applications]. It makes you really think hard to carry out meaningful research.

Hughes: Grant applications are peer reviewed. That was not true in Holland? How did the money come?

Heyneker: It was not by writing grants. Let's say, radiation biology and genetics in Leiden as a department was awarded some money. I figured my professor, Professor Rorsch, probably had to fight reasonably hard to get the money, but then—pfffttt.

Hughes: That was a pot of money.

Heyneker: Exactly. So that made life very easy for us. And here in the United States, it was much farther disseminated—each professor has to find his own pot. But therefore, you buy also your independence. So that's why Herb Boyer didn't have to be nice to the head of the Department of Microbiology. He brought his own money, which is very useful. Look, I fell in love with it. I felt the system was very good, very efficient, I found the quality of the research just—I was in awe. It was such a learning experience for me, okay. It was the best thing that could happen to me. It brought me to the next level.

More on Heyneker's Lac Operator Research

Hughes: Do you want to talk about the specifics of the work on lac operator?

Heyneker: [laughs] Sure. Well, this is an example how successful we were and how things came together so nicely. I started to work on lac operator I think in February of 1976, and by April we had done it. That was a team effort: Keiichi Itakura provided me with the correct oligonucleotides, and we put them together with ligase, and we had a good plan. And Paco Bolivar had built a very useful plasmid. Not just Paco Bolivar; I should be honest here. It was Mary Betlach who had built this wonderful plasmid which you could use to shuttle pieces of DNA in and out. That was called pMB9. MB stood for Mary Betlach. Paco Bolivar built on pMB9, and he eventually came up with plasmid pBR322. The uniqueness of that plasmid was that it had a positive and a negative selection. It had two antibiotic genes cloned in it, so if you would clone a piece of DNA in one of the genes, you would knock out the function of that gene, but you kept the function of the other one. So you had always a positive/negative selection to help you prove that you had the right insert. It is an example of how important it is to work together when people do different aspects of the overall project.

So by April, we had the lac operator cloned. And I think it had significant implications. It paved the way for larger and bigger and better projects. But also it was the first example that DNA which was chemically synthesized from off-the-shelf chemicals could be stitched together and then inserted in the plasmid. [tape interruption]. Then the plasmid will be transformed into bacteria, and the bacteria will divide, and the plasmid will divide, and you basically immortalize your piece of chemically synthesized DNA, so you multiply the DNA. It's a very strange concept: you create a biologically active entity, and it is a very small beginning because this piece of DNA is merely coding for the lac operator. But the function in bacteria is that it will become constitutive for beta-galactodsidase expression. So there is this biological activity.

Extrapolating from here, the next thing you can do is synthesize an entire gene and perhaps later you can synthesize the DNA coding for the entire microorganism, not that we were thinking about that in those days. But now it is so easy to make DNA and there are such clever ways to stitch synthetic DNA together, to synthesize a gene is way faster than trying to fish it out from bacteria. If you want to make DNA for an entire virus, it can easily be done, with all advantages and potential disadvantages.

Hughes: In 1975, and maybe a few years before, people were already thinking about and doing gene synthesis. Isn't that what Khorana had done in 1970?

Heyneker: He did that at almost the same time we did it. He did do a lot of work with the process of DNA synthesis, but his using these oligos to make a gene was really almost the same time we did somatostatin. It was never his research direction. It was only later that he became intrigued by doing this.

Heyneker's Research on RNA Ligase

Hughes: So very quickly, by April you say, you'd essentially done the lac operator. So then what?

Heyneker: What I did next was a project together with Howard Goodman. I'm not sure this is worthwhile discussing, but what I found is that when I purified my DNA ligase and I used an assay which measures pyrophosphate exchange, I found a second peak which came off the column after my DNA ligase peak. I was always intrigued what that was, and we determined that it was RNA ligase. So since you purify your DNA ligase, you might as well also collect your next peak. So I had this purified RNA ligase, and we did some experiments to prove that RNA ligase was extremely helpful in blunt-end ligation.

Hughes: Were you working at the bench with Howard Goodman?

Heyneker: Well, I was working at the bench with a visiting scientist in Howard Goodman's lab, Nicholas Cozzarelli. His name is probably familiar.

Hughes: Yes, it is. This was a project that had been conceived of by Howard?

Heyneker: Well, I think it was conceived by me.

Hughes: Oh, sorry.

Heyneker: No, not sorry. It was a slight problem because it was later determined that I should not be first author of that paper, and I never like that a lot. It was definitely my idea, but *c'est la vie*.

The Boyer-Goodman Collaboration

Hughes: You're not the first one to imply that Howard Goodman was not the easiest person to deal with.

Heyneker: Right, although in general I didn't have a problem with Howard. More indirectly did I have a problem listening to the tales of Axel Ullrich, Peter Seeburg, John Shine, and Herb Boyer. It's a little bit sad, because in academe there is so much pressure to produce and be recognized as a lead scientist that often there is not enough room for two. It was clear that Boyer and Goodman needed to find their own identities, and often that doesn't work; such a separation is not always amiable. I can understand the difficulties because of course Howard Goodman and Herb Boyer were principal investigators, and they needed to establish their own identities.

Hughes: Do you know why that close collaboration originated? Was it strictly scientifically based?

Heyneker: No, I think they were also very good buddies. And that ended. It was very sad.

Hughes: I understand that the agreement between Boyer and Goodman was that both their respective names appeared on every publication, and that became a problem on one of the recombinant DNA papers, namely the *Xenopus* paper.

Heyneker: Why did that become a problem?

Hughes: According to Stan Cohen, Goodman hadn't done much.

Heyneker: So he was piggybacking.

Hughes: But also Boyer told Stan that the agreement was that Goodman's name was to appear on any paper along with Boyer's. At least that's the way I've heard it.

Heyneker: Well, that doesn't surprise me. They were good friends.

Hughes: I think Goodman had done something—maybe supplied an enzyme. It wasn't as though the demand was completely groundless.

Heyneker: Well, he's very smart. Probably he will also have made intellectual contributions. I was much more bitter with Howard early on than now. I think looking back you can see things probably in a little better perspective than you see when you're a hotheaded postdoc and you're fighting for your place.

Hughes: You talked about Boyer and Goodman needing to establish their identities. Well, that is what postdocs are trying to do.

Heyneker: Absolutely. That is why first authorship is so important.

Goodman's Problem with His Postdocs

Hughes: But also, here's this new science breaking loose, and people seeing the tremendous potential and maneuvering to maintain a high profile and in a small space.

Heyneker: Don't forget Howard was on the ninth floor, so from that point of view he had his own independence. Howard was in Japan for a sabbatical, and at that time his postdocs, Axel Ullrich, John Shine, and Peter Seeburg, made some very important discoveries, like they cloned the insulin gene. So Howard rushed back to take control of the lab again. He did that sort of clumsily I would say, and therefore he lost a lot of friendship with those people. It was very unfortunate, and it was not necessary in my opinon, but it all had to do with who is getting the recognition for the work. In the eyes of postdocs, they felt that Howard was probably getting way too much recognition because the work was done while he was not even in the lab.

On the other hand, Howard Goodman made it possible by attracting these people to his lab to get the work done. What is the balance? The sad news is that Howard Goodman could have been much cleverer about it and much more diplomatic and created a win-win situation. I think his social skills got him in this trouble. I do like him as a person, and I think he means absolutely well, but it was a vicious time. And here's the situation: Recognition is the only outlet in academe for your work. In industry, if you make a nice invention you get a whole bunch of shares, to say, "Look, I recognize your contribution, and you know what? I'm going to reward you for it." In academe you don't have that outlet. It really is how to inflate your name, how to become a very well-recognized person. And that can have some very negative effects. It is a disincentive to collaborate, to a certain extent, and it creates sometimes there problems. I feel sorry about it.

Tensions Over Patenting

Hughes: Another thing beginning to occur in the years that you were at UCSF is the movement on the part of the university towards greater interest in intellectual property. Patents were applied for, and the postdocs felt that their contributions were not properly acknowledged because on some patent applications their names didn't even appear, and it was the lab heads that were the inventors.

Heyneker: Right. It depends very much on the definition of inventorship, and that is a moving target. For instance, you can jeopardize a patent by putting too many people on the patent—people who carried out the work, but the invention had been made by somebody who said, "Look, do this, that, and the other thing." So the inventor comes up with the idea, and a technician or a postdoc can reduce it to practice. It depends very much on how that is interpreted by the law firm and by the patent law. So, yes, patenting created a lot of potential tension and unhappiness for the postdocs, but it is also probable that the postdocs did not understand exactly how it works. It is not the same as putting your name on a paper.

Hughes: Yes, and that's probably what they were equating patenting with, wasn't it?

Heyneker: Right. Currently there is a tendency to put more names on the patent, so reduction to practice is now being viewed more as you are therefore a co-inventor. In the early days it was more, hey, who made the invention? I was to a certain extent involved in this situation myself. I don't think that my name was on the somatostatin patent, although it was on the paper. And I have no real problems with it because it was not my idea. But I did make a significant contribution to reduce the idea to practice.

Hughes: Nowadays would your name likely be on that kind of patent?

Heyneker: I think probably yes.

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Hughes: I've heard that in the biological sciences, which of course would mean virtually all the research that UCSF was doing, that patenting wasn't the first thing that sprang to people's minds probably as late as the late seventies or even into the eighties.

Heyneker: I don't know enough about that to give a meaningful answer here. I think Stanford was much more savvy than San Francisco, and I think UCSF is quite lucky that they got Boyer-Cohen patent money.

Effect of the Recombinant DNA Controversy

Hughes: We have danced around this political and social context, which was escalating in the years that you were at UCSF around two themes: the possible biohazards of this new technology and, at a slightly later date, the appropriateness of academic research being commercialized. How aware were you, if at all, before you arrived in San Francisco that there were some questions developing around this new technology? Was it a discussion point in the Netherlands?

Heyneker: I don't think that when I left Leiden to come to UCSF that that was an issue. I take that back because Asilomar had already taken place—right?

Hughes: What month did you come?

Heyneker: November of 1975.

Hughes: The Asilomar meeting occurred in February of 1975.

Heyneker: I can't recall how much of an issue it was at that time in Holland. I think there was no recombinant DNA work going on in Holland at that time. It was really only done by a very small group of people elsewhere who had the tools. Coming back to Holland after two years, going back to the university because that was my obligation, I found myself in a situation that recombinant DNA research was almost banned. We were very worried about the potential dangers of recombinant DNA technology. A government guideline advised us not to be involved in recombinant DNA technology. It did not go as far as to forbid it, but they only wanted to do certain aspects of recombinant DNA technology

which were absolutely not dangerous—like staying in the same species, for instance. Coming back to the Netherlands with this treasure trove of information about recombinant DNA technology, where a lot of people wanted to collaborate with me. There was a guy from Finland, Mattie Servas, who wanted to come to Holland to spend a few months with me, and he had to go back after a week because we tried to clone some genes from *Bacillus subtilis* into *E. coli*, something which nobody would have any problem with it, but this was enough in Holland to stop this type of research.

Hughes: It wasn't a question of building a P3 lab or whatever—one just didn't do the research?

Heyneker: Right. Well, P3 labs were being built in Holland then, but I never felt that cloning from one bacterium to another was dangerous, although there was very little knowledge about exchange of genetic information between different bacterial species. Now we know that bacteria exchange information all the time. But in those days it was not known, and people were cautious. That was the main reason for me to go back to the United States in short order. But again, I'm ahead of the story.

Hughes: If you were reading *Nature* and *Science* magazines, it was hard to escape the fact that there was a political controversy surrounding recombinant DNA.

Heyneker: Oh, absolutely, there were those guidelines, sure.

Hughes: Did the controversy engage you?

Heyneker: Engage is a strong word. I found it a real drag because it was putting a string on the research that could happen. For instance, when we did the work on somatostatin, we had to do the experiments in a P3 room.

Hughes: I was thinking of the situation earlier than that, around the time of the Asilomar conference. You could have said, "This controversial area of science: I'm not going to touch it! I'm going to go back to DNA repair or something."

Heyneker: Well, perhaps I was too naïve. I found it very interesting, important research. I really felt it was giving us some answers. I never felt that I wanted to give up on it.

Hughes: Did you think that there was any basis for concern?

Heyneker: [pause] Well, yes. We could see, for instance, having *E. coli* produce a human toxin, and then the chance that this *E. coli* would colonize your intestines, that we felt, my goodness, that could be a little scary. The idea that you could synthesize an entire viral DNA was absolutely not in the books. That was so futuristic; we were not thinking about those sort of things. We could imagine some complications, and one of the reasons why we decided to focus on expression of somatostatin at a fusion protein was it gave us peace of mind. We felt the chance that it could have biological activity was negligible. It's not the only reason—I have to be very fair and honest: when we tried to express it directly we didn't get anything, so there were other reasons why we ended this fusion protein. But one of the reasons definitely was peace of mind, because we felt if we made a bacterium which made a lot of somatostatin, and that bacterium colonized your intestinal flora, we might get an imbalance of hormones, of somatostatin.

Hughes: What effect, if any, did the research moratorium and later the NIH guidelines have on the research that you and others in the Boyer lab were doing?

Heyneker: Well, they had some effect, but a lot of research people did was not affected. For instance, the work I just explained on RNA ligase, DNA ligase, could go on, no problem. Also, the construction of plasmids could go on without a problem. The expression of foreign genes was the aspect that made it a little harder. UCSF built a P3 facility, and whenever we had to do some experiments, we went there. That was not our first choice, but we did follow the guidelines.

Hughes: Did you work quite a bit in the P3 facility?

Heyneker: Not that much. I don't think I did the experiments with the synthetic lac repressor in a P3 room. It was the same species. But somatostatin, yes, we did some of the work in P3, definitely.

The Somatostatin Project in Boyer's UCSF Lab

Genesis of the Project

[Interview 3: April 9, 2002]##

Hughes: We've skirted around the somatostatin work, talking about the context in which it and other science was done in those years you were in Herb Boyer's lab. Perhaps you could start today with how the somatostatin work began in the UCSF lab and what your role was.

Heyneker: The somatostatin work started as a collaboration between the lab of Art Riggs, the lab of Keiichi Itakura, and the lab of Herb Boyer. Herb and Art knew each other from earlier days and respected each other. Art came to Herb with this proposal. Art had written a proposal to get a grant from the NIH. The grant was not approved.

Hughes: Do you know why?

Heyneker: Well, what I understand is that they didn't believe that the work could be done in such a short time frame with so few funds. And they didn't understand exactly what the relevance of this type of research was.

Hughes: Do you suppose that Riggs had proposed it as a basic science research question?

Heyneker: Yes and no. I think he proposed it as a proof-of-principle concept, to demonstrate it was possible to express in bacteria a product which is normally not expressed in bacteria. He did not choose somatostatin because he saw some commercial relevance there. It was a peptide hormone which had been sequenced recently and some of the biology became known. He wanted to start with some small peptide hormone which had some biological

activity so that it could be demonstrated that indeed *E. coli* could do this, manufacture a human hormone. But I think he had in mind, if it did work, he was going on to bigger and better things, like insulin. Already at that time, insulin was definitely somewhere in his mind.

Hughes: With practical application in mind?

Heyneker: I think so. Also, when we started this work was the time that Genentech came into the picture. I remember that Bob Swanson was questioning whether we should do somatostatin—why not work directly on insulin? It was Art Riggs and Herb Boyer who convinced Swanson to take the time, that he would learn a lot from somatostatin, that insulin was significantly more difficult, and that we probably could use the knowledge gained from the work on somatostatin. I'm not sure if I say this in hindsight, but I do remember that over the objection from Bob Swanson we started to work on somatostatin first. Therefore, I believe, very early on, there was already the idea, what's next? What comes after somatostatin? I think it was in hindsight a very good decision because we learned a lot from the somatostatin project, namely, that it was not so straightforward to express this peptide hormone in *E. coli.*

Hughes: Did you ever think that it would be straightforward?

Heyneker: Possibly, yes. I probably was naive enough to think, if you have a promoter and if you have a gene and you hook those two things up, you make a product. These were new times—not that much was known about the organization of genes. Also, not much was known about how the translation machinery of *E. coli* takes care of small peptide hormones.

A Setback in Expressing Somatostatin

Heyneker: One lesson we learned in the process is that *E. coli* degrades small peptides very rapidly. Therefore, yes, that definitely set us back to a certain extent.

Hughes: I can remember Bob saying to me how he saw his company and his own career going down the drain when at some point he went down to City of Hope, and the experiments that were supposed to be producing somatostatin—

Heyneker: Showed nothing.

Hughes: —showed nothing.

Heyneker: I remember clearly that Bob Swanson was at least once a week waiting for us in the back of the building—there was a little patio where we could meet.

Hughes: At City of Hope?

Heyneker: No, this was at UCSF—to get an update on where we were. Bob was, rightly so, extremely impatient and extremely anxious for us to get results. Indeed, the early results

were disappointing, and we demonstrated that the reason was that the protein probably was degraded. We obtained some proof of that. Also, it was in the literature; there was definitely some work presented by the group at Cold Spring Harbor. Anyway, this group at Cold Spring Harbor [Bukhari and Zipser] did some good work on demonstrating that small peptides were degraded very rapidly in *E. coli* by *E. coli* proteases.

Hughes: Why wouldn't that be obvious?

Heyneker: [pause] No, I don't think at that time it was obvious.

Hughes: But a protease is a protease, right?

Heyneker: Well, proteases have some specificity. At the same time, proteases are not degrading the proteins; they are degrading small subsets of the protein. A peptide is a very small protein, between five and fifteen amino acids. It is a piece of a protein which probably does not have a lot of secondary structure by itself. That's probably one of the keys why those sorts of products are being degraded. It will help *E. coli* for housekeeping reasons to do that. At the same time, it's a little more complicated because bigger proteins, which do have tertiary structure and are really full of internal globular domains, ought not to be degraded, otherwise it would be terrible for the bacteria.

The Original Experimental Plan

Hughes: What parts of the somatostatin experiments were actually done at UCSF in Boyer's lab, and what parts were done at City of Hope?

Heyneker: Because the project was started by Art Riggs when he came on sabbatical to UCSF, he wanted to start this project and start with the cloning project. I liked Art Riggs, and I was assigned to help Art to work it out. Plan A, the first plan, to express somatostatin was different from the way we did it eventually. The original plan was to express it directly as somatostatin.

Reasons for Choosing Beta-galactosidase

Heyneker: But there were some problems with the design of the experiments as well as some anxieties that making somatostatin in *E. coli* could be undesirable because, after all, *E. coli* inhabits the intestines and is part of our natural flora. We were definitely aware of the possibility that an *E. coli* which was produced with somatostatin could affect the biology of the human system. So quite soon thereafter we changed the plan to make somatostatin not directly, but to make it as a fusion protein, which means we were going to borrow some of the sequence from an enzyme called beta-galactosidase. You would stitch the gene for somatostatin behind a portion of the gene coding for beta-galactosidase.

Hughes: Whose idea was that?

Heyneker: I recall that it was Art Riggs's idea.

Hughes: Why would that have been an obvious thing to do? Why beta-galactosidase?

Heyneker: I don't want to say it was obvious. I think it was a smart thing to do, because it solved the problem that you could not make somatostatin directly. We were convinced that if you made a combination of beta-galactosidase and somatostatin that it would not have biological activity. It solved the potential problem at that time that we would make something which was undesirable. Also, from a practical point of view, we knew that there was a very convenient restriction enzyme site early in the beta-galactosidase gene because the gene had been sequenced by the lab of Wally Gilbert, and we had access to that sequence.

Hughes: It had been published?

Heyneker: We might have had access to it before it was officially published, which happens often—pre-prints or whatever.

Hughes: Why was the restriction site convenient?

Heyneker: Well, because we did not have to change too much in the plan of synthesizing oligonucleotides coding for somatostatin. That required that we started with a four-base overhang which was in register with the EcoR1 site. Let me go back. It was not an EcoR1 site; it was a HaeIII site at amino acid seven or ten, somewhere there early on. We could very conveniently convert that HaeIII site into an EcoR1 site with the tools which were available to us in 1976-77. So once we made an EcoR1 site at that position, then subsequently to clone in the somatostatin gene became quite doable. So that was the practical reason.

Removing Methionine

Heyneker: There was also another practical reason, namely the first amino acids of each protein which had been expressed in *E. coli* start with methionine because you start with ATG, the so-called initiation codon. That is the dogma: every protein in *E. coli* starts with an ATG, with a methionine. Now, the methionine can stay on the protein or the methionine can be removed by an enzymatic process; it doesn't matter. But the gene always starts with ATG. So, in our synthetic scheme, we started also with an ATG, which was methionine, but the eventual somatostatin is a peptide hormone without methionine. The beauty of the experiment was that we could isolate this peptide which was a mixture of beta-galactosidase plus somatostatin with the methionine somewhere in the middle. There's this unique chemical step you can do, treating this peptide with cyanogen bromide which recognizes methionine and cleaves at the methionine, taking the methionine off, leaving you with the final product. So all of a sudden we did not have to express somatostatin directly; we could express it as a fusion protein because later we could fix it and end up with just somatostatin.

Art Riggs, Herb Heyneker, Keiichi Itakura *photo courtesy of Herbert L. Heyneker*

Circumventing the Problem of Peptide Degradation

Hughes: Is the fusion protein also related to the problem you had with the bacterial proteases chewing up the somatostatin?

Heyneker: Absolutely. It turned out that when we made what we called "the short fusion" because it was only a very small piece of beta-galactosidase, we used only the first, I think, seven amino acids of galactosidase. I think there are fourteen amino acids in somatostatin, so it was a piece with twenty-one amino acids. It's still very short, still considered a peptide. Here we're coming back to Bob Swanson's anxiety. When we were checking if we could detect somatostatin in a radioimmune assay, we could not detect anything with this short fusion protocol, although we knew that we had the right sequence because after we cloned a synthetic fragment coding for somatostatin it was sequenced, and we proved that the sequence was correct.

Hughes: What did you think when the assay came up with nothing?

Heyneker: [pause] Well, we were a little bit worried about it already. The fact that peptides were being degraded in bacteria was not something totally unknown to us. So I think I was disappointed.

Hughes: But you remarked at the beginning that you were somewhat optimistic about your ability to express somatostatin in *E. coli.*

Heyneker: Well, I said I was naive, okay?

Hughes: You knew that bacteria were known to chew up peptides.

Heyneker: Well, nobody knows if all peptides are chewed up, or how the mechanism really works. It was definitely worth a shot—let's put it that way.

Hughes: How much of this were you telling Bob? Was only selective information flowing from the scientists to Swanson? He was not a scientist.

Heyneker: I don't think so, no.

Hughes: So there wasn't a discussion: "We may be able to produce the protein but we don't know whether the bacteria will chew it up." Then Bob goes through the ceiling and says, "Why am I funding this research?"

Heyneker: Right. I think I was probably sheltered quite a bit from these types of discussions. I bet he had those discussions with his co-founder Herb Boyer more than with me. But luckily we had plan C, right? And that was to make a long fusion, which means to put somatostatin all the way at the end of the beta-galactosidase.

Hughes: You had formulated those three approaches from the very start?

Heyneker: Absolutely not. Plan C came when plan B didn't work. [laughter]

Hughes: C follows B.

Heyneker: Right. Well, there was no plan D because C worked dynamite.

Hughes: This might otherwise have been a very long oral history. [laughter]

Heyneker: Right. [tape break] We did not stop the project. Somebody told me, and I think it was Herb Boyer, and I think it was Art Riggs who discussed this with Herb Boyer, that perhaps we should try another tack, namely to put the gene coding for somatostatin at the end of the beta-galactosidase gene. What I recall is that Herb Boyer said we should bury it at the end of the beta-galactosidase gene.

What we also learned is that at the end of the beta-galactosidase gene there is an EcoR1 site. And we needed an EcoR1 site to put the somatostatin gene in. We were lucky because that EcoR1 site was exactly in the same reading frame as the EcoR1 site which we put in at the beginning of the beta-galactosidase gene. So the experiment was quite straightforward, and I don't want to go into all the scientific details because you can read it, but without too much work we could make this long fusion. And when we treated the long fusion with cyanogen bromide, and we analyzed the peptides in a radioimmune assay, it was crystal clear and without a doubt that we made significant amounts of somatostatin. Between the first failure and the next success I don't think there was more than a month or at maximum two months. I would say within a month we had it.

Hughes: Herb wanted to bury, to hide, the somatostatin, from the proteases?

Heyneker: Yes, well, the big protein would fold in this three-dimensional structure, in a globular structure, and, indeed as you say, it would serve to protect or hide the somatostatin fragment which was tagged on to the 3-prime end of the beta-galactosidase. Zabin was the first to work out the amino acid sequence of beta-galactosidase.

Hughes: That's what gave Herb the idea?

Heyneker: I'm not sure if it was Herb's idea or if it was Art Riggs' idea. I heard it from Herb, but I think that Art had discussed it with Herb.

Hughes: I still don't understand why beta-galactosidase rather than another protein was chosen.

Heyneker: A sequence of approximately a thousand amino acids is no longer a peptide. It has definitely a three-dimensional structure. We would have been greatly surprised if a big protein like that would be degraded.

Ligation of the Synthetic Oligonucleotides

Hughes: Who was doing what for the somatostatin project?

Heyneker: Well, the DNA synthesis was done by the lab of Keiichi Itakura, not just by him alone but by his group. I think Roberto Crea was there. DNA synthesis in those days was clearly

not a straightforward enterprise. It was a lot of hard work. It was a challenging chemical synthesis, and it sometimes went right and sometimes went wrong. I struggled quite a bit with the oligonucleotides I received from Keiichi Itakura's lab. I think that he sent several batches of different oligos.

Hughes: Why did you struggle?

Heyneker: Well, to stitch them together. We could not synthesize the entire gene with one oligo; it was built up from short oligonucleotides, and each oligonucleotide was fourteen bases in length. Four oligos represented the top strand; four oligos represented the bottom strand. I think it was that way. I think we ligated them in two groups. The first four were ligated, and the back four were ligated. Then we mixed the two, and we ligated those together.

Hughes: That was your job?

Heyneker: Yes, that was my job.

Hughes: You were Mr. Enzyme.

Heyneker: Yes, well, that was my job, exactly. It was not that difficult. I labeled those oligos in the kinase reaction with P_{32} so I could follow the reaction on the gel. And then I added ligase and I would see what was happening. And if something happens it is quite dramatic—you clearly see a shift on the gel. So you don't have to guess too much. And if the oligos were good, it was easier to see this shift than when the oligos were bad.

Hughes: When the oligos were bad there were mistakes in the sequence?

Heyneker: Well, no, more that the quality was bad. It was a mixture of shorter products, and also a mixture probably with chemicals left in there, so the enzyme didn't have a good time. After all, enzymes are quite finicky. They work great in a biological environment, but they're not meant to work in a harsh chemical environment. So if there are some harsh chemicals left behind, I can imagine that the enzyme might not work or not work properly.

Hughes: Was the result that you had poor ligation?

Heyneker: I don't want to go that far that it was a huge struggle. It took some time. What you would now do in an afternoon without any problem was definitely a work of a couple of months to try and try again and try again.

Hughes: Was there a lot of dialogue between you and the DNA synthesis people?

Heyneker: Now and then, yes. If you had to resynthesize it, you didn't get it the next day. It was for them also an enormous chore to do it again. It might take a couple of weeks before we got the next batch.

Cloning and Sequencing Somatostatin##

Heyneker: I ligated those fragments, analyzed the results and the product by gel electrophoresis, and then cut out the band of the right size and cloned it. That was all good and fine. But the real challenge was to demonstrate that the sequence was right. We obtained a few clones, and we analyzed I think half a dozen by doing the Maxam-Gilbert sequencing reaction. I have to mention here that my good friend John Shine played a very significant role because he had acquired that technology from Wally Gilbert, and he was the first to do it and try it out and work on this in the lab of Howard Goodman. So we read a few gels, and I recall it was only one clone which was exactly correct.

Hughes: Really!

Heyneker: You only need one, right? One out of four or one out of five, something like that. And the rest were either short or they had something wrong with the sequence.

Hughes: Shine was the sequencing person, and you were the ligating and cloning person?

Heyneker: Well, Paco Bolivar was also the cloning person because he provided the plasmids. I mentioned that one of the reasons we were so successful at UCSF is that we had all the different disciplines and different expertises which we brought with us or we acquired them there. There was a good division of tasks.

Hughes: You didn't have DNA synthesis capability in Boyer's lab.

Heyneker: No. DNA synthesis was done at City of Hope.

Hughes: But that's important, isn't it?

Heyneker: Absolutely. Critical.

Hughes: But it also explains why you bothered to collaborate. Otherwise you would have done all the research within your own lab.

Heyneker: Otherwise, yes.

Richard Scheller's (Non-)Role

Hughes: How does Caltech and Richard Scheller fit into the story?

Heyneker: I don't think they fit here. They fitted earlier when we were doing the lac operator project. Caltech was very interested in the lac operator because they combined lac repressor to it, and then they could crystallize the lac repressor in the absence and in the presence of this piece of DNA and learned a lot about the interaction between the protein and the DNA. By the time Keiichi Itakura did the somatostatin work, he was already at City of Hope where the synthesis was being carried out.

Hughes: Richard Scheller made an attempt to synthesize some DNA for the somatostatin project. Or he provided linkers—I forget which.[1]

Heyneker: He came to Herb Boyer's lab to play around with the linkers. The linkers were provided by Keiichi Itakura, but I think they were also provided by another collaborator we had. Who was it? Such a nice guy.

Hughes: I saw the name Wiley Vale who was at the Salk Institute.

Heyneker: Wiley Vale sequenced the somatostatin protein. No, this was Schildkraut, I think. He provided us very early on with very short oligos which contained the EcoR1 site. There were two complements of each other, so you only had to synthesize, let's say, one ten-mer and they would perfectly match on top of each other. They played very important roles in our early research. For instance, if we wanted to change the HaeIII site, which I mentioned, into an EcoR1 site, we used synthetic linkers to accomplish that. Rich Scheller came to Herb Boyer's lab—I think he was still a graduate student. Was he at Caltech at that time?

Hughes: He was in Richard Dickerson's lab at Caltech.

Heyneker: He came to Herb Boyer's lab to learn ligation with these linkers. We put those linkers on the lac repressor to get them cloned in *E. coli.* So linkers played a very important role early on in cloning research to facilitate cloning, to make it easier. But to say that Rich Scheller played a role in the somatostatin project, I can't recall that, and I'm 99 percent certain he didn't.

Hughes: I think he played an aborted role. He was supposed to provide something for the somatostatin project, and it didn't work. The reason I say that is that at the time of Genentech's IPO there was a headline, and I think it was in the *L.A. Times,* saying "Graduate Student Turned into Millionaire," or something along that line, and it was because Scheller had been given shares in Genentech which at the IPO escalated in value.

Heyneker: That's very well possible. I don't dispute it at all, but he did not do anything on the somatostatin.

Heyneker's Decision to Stay a Second Year at UCSF

Heyneker: Art Riggs and we were unsuccessful at doing it, which was plan A, so then we started over with plan B. By that time Genentech offered me a stipend so I could stay an extra year at UCSF because my grant from Holland was good for only one year. They did agree that I could stay an extra year, but I had to find my own money. As you may recall, a job was waiting for me in the Netherlands when I would come back. So they were willing to keep that position open so that I would have a job when I came back, but they

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1. As a graduate student in Richard Dickerson's lab at Caltech, Scheller was paid by Genentech to synthesize the gene for somatostatin but failed. See the oral history with Scheller in this series.

were not willing to pay me for a second year. So Genentech filled in the blank and paid my salary.

Hughes: Was it a given that you would stay?

Heyneker: Oh, when I could do this work, absolutely. I wanted to stay, absolutely wanted to stay, an extra year. This was too exciting to give up.

Hughes: How did your wife feel?

Heyneker: I think she wanted to go back to Holland, but I did not have a hard time to convince her to stay. I think California was exciting enough and the weather was great. She had young children. We lived in Burlingame at that time.

Hughes: Oh, you had moved out of the city.

Heyneker: Yes, quite soon. I think we stayed in the city for only three months, and then a Dutch couple we got to know moved out of their house in Burlingame, and we moved in. So I started to commute from Burlingame. I think it was a good decision, especially with young kids, because there we had a little yard and so on. It was quite nice.

Hughes: Did you hear discussion about getting approval from the Recombinant DNA Advisory Committee for the somatostatin work?

Heyneker: Before we even started it?

Hughes: Yes. I assume that it had to be approved.

Heyneker: Well, what I recall vividly is that when we had to show that we were making somatostatin, the cyanogen bromide work and so on we did in a P3 facility. I can't recall it for sure—we probably did the cloning experiments in the P3 facility. If we needed approval at the time, and we touched on this before, I'm not sure about it—I think synthetic DNA was exempt at that time. However—and I want to reiterate—we were definitely aware of what we were doing, and we were apprehensive about the expression of somatostatin directly in *E. coli*. So when we could do the same experiment using a fusion protein approach, we were very comfortable that we were not doing anything which was against the guidelines.

We were lucky. The somatostatin gene did not contain any methionines, so we could use this chemical cleavage trick with cyanogen bromide. As a matter of fact, the A-chain and the B-chain of insulin don't contain methionines either. So we could use exactly the same protocol, the same strategy, to obtain the A-chain and B-chain from insulin. I mention it now because earlier on in our discussion I mentioned that although somatostatin was a proof-of-principle project, you learned an enormous amount from it which we could use very nicely for the next project.

Controversy Over David Gelfand's Contribution

Heyneker: Let me bring up a controversy. We knew from the literature that there was an EcoR1 site at the end of the beta-galactosidase gene. And the gene coding for beta-galactosidase was being sequenced, I think by Zabin's group. David Gelfand was in the UCSF Department of Biochemistry, in the lab vacated by Gordon Tomkins when he passed away. He was a good colleague of mine, and I did a lot of talking to him, explaining what I was doing, and he was explaining to me what he was doing. So he was aware of the experiments we were doing. He provided me with the information on where exactly the EcoR1 site was in the beta-galactosidase gene. I learned that the frame of that EcoR1 site was the same as the frame of the EcoR1 site we put in front of the beta-galactosidase gene. It made our life easier because there are three reading frames because DNA is read as triplets, so if you are one base out of frame, you read different triplets. There are three possibilities. So we had a 33 percent chance that it was the right frame. Based on the amino acid sequence and also knowing that there was an EcoR1 site at the end, Dave Gelfand could deduce where it was. He also knew what the reading frame was, and the reading frame was the same. It helped us—not helped us—it made our life easier, let me put it this way, because we knew exactly what to do, and we could do the experiment very quickly. Hence we had the results soon after we had the original results.

Now, here is where the controversy started, and it's a little bit sad because Dave claims that he made a very significant invention in the project by letting me know what the reading frame was for the EcoR1 site. In many disputes between Genentech and UCSF, it was always brought up what an important contribution it was. I've never felt that way. If it was not the right reading frame, we would very quickly get the right reading frame.

Hughes: Because you had only two other possibilities.

Heyneker: There were only two other possibilities, so it was a matter of using some synthetic DNA or whatever to get it in the right reading frame. I always felt it was a helpful contribution, but absolutely something we could have done without. Moreover, the DNA sequence and the amino acid sequence came along very quickly. And I think independently Art Riggs in the meantime had also deducted from the amino acid sequence where the EcoR1 site was. I still feel a little bit bad about it because it definitely influenced my friendship with Dave Gelfand, which was not necessary. It was almost an unsolicited observation he gave me. I didn't ask him for it; he gave it to me, as if I was contaminated now with this knowledge. And I really didn't need it, but having it and in the spirit of scientific collaboration, good; it was helpful. So for the record, I want to explain my feelings.

Hughes: When did the issue first arise?

Heyneker: I can't recall exactly, but it had to do with the contributions of other members of the UC team.

Hughes: In terms of litigation.

Heyneker: Yes.

Hughes: You're referring to the recent case between Genentech and UC?

Heyneker: No, I don't think so. There were litigations going on—

Hughes: All along. [laughs]

Heyneker: All along, yes. Since it had to do with plan C, with the long version, I feel this is a good moment to bring the subject up.

Hughes: Absolutely.

Convergence of Basic Science and Commercial Application

Hughes: With the success of the somatostatin work, it was becoming apparent that this technology had practical applications. Was there immediate interest in commercial applications?

Heyneker: [pause] Well, it was definitely a bombshell when we announced it. The news came to the Senate very quickly, and they realized that this was a significant development. If you have the opportunity to make very precious products all of a sudden in unlimited amounts in bacteria, it opens the door for a lot of applications. Especially insulin was a logical candidate, because insulin until then was being derived from pigs and cows to a certain extent. With the increase in the number of diabetics and the limited supply, people could see that it was becoming problematic, definitely looking into the future. And to have an alternative was very helpful. So I think it was probably a very political issue therefore.

Hughes: Was there discussion at the level of the postdocs?

Heyneker: Well, I think so, because in Howard Goodman's lab, Axel Ullrich, Peter Seeburg, and John Shine were working hard to clone useful genes—useful for commercial applications, like the insulin gene and the human growth hormone gene. So that was happening at the same time that I was cloning a synthetic gene. So yes, there was an awareness that this sort of technology could work commercially one day.

Hughes: Was the emphasis beginning to shift from basic science to practical application?

Heyneker: Yes and no, because I think when you do something for the first time, you can call it just as much basic research as you can call it applied research. So proof-of-principle to do something for the first time and demonstrate that indeed it is possible to express in *E. coli* a chemically synthesized gene or later a gene which comes from a eukaryotic source was never done before, and there were a lot of voices arguing that this might not be possible. For instance, the difference between prokaryotes and eukaryotes might well be in differences in codon usage between prokaryotes and eukaryotes and also that eukaryotic cells would use different rules for DNA expression. So it was not an obvious thing that you could express heterologous genes in *E. coli*.

Hughes: You're saying quite clearly that the basic science aspect was at the forefront.

Heyneker: I consider the somatostatin project to be to a large extent basic science.

Hughes: Then why was there criticism—

Heyneker: Although at the same time I was funded by Genentech, which means that Genentech looked a little farther ahead: hey look, if this works, this forms the basis and the foundation for more practical applications. So perhaps you are right that the research was already more applied. I see here a convergence of basic research and applied research.

Hughes: At what point do you say that basic research has become applied? It's a continuum.

Heyneker: Absolutely, yes.

Hughes: So would you say that criticism was leveled not so much at the science, which could be interpreted as still being on the traditional academic mission, but at the fact that corporate money was finding its way into an academic laboratory?

Heyneker: The fact that corporate money was flowing into the lab was probably more of a concern than whether you were doing pure research or a little bit less pure research.

Heyneker's Abiding Enthusiasm for Applied Research

Hughes: Did you feel the heat yourself because you were one of the recipients of Genentech money?

Heyneker: I understood that we were going in the direction of applied science—I loved it! I had never for one moment a problem with it. I definitely raised my hand—I asked to be involved in the somatostatin project. It was so fascinating. The fact that I could use bacteria as little fermenters to make valuable products was extremely appealing to me. I was not thinking at all about the money in those days. It was the fact that we could make medicines this way—that was fascinating to me. And still is.

Hughes: What is it that made it more than okay for you to accept this situation, not only accept it but to ask for it?

Heyneker: And embrace it.

Hughes: Others expressed criticism. No way were they going to get involved with recombinant DNA.

Heyneker: Well, first of all, they were not asked to be involved. That is perhaps a good starting point. [pause] I think there was perhaps some misunderstanding. I felt that I was doing quality science. I don't want to differentiate between so-called basic science and applied science. You need the same sort of rigor to do both.

Hughes: Did you really think that at that point?

Heyneker: Absolutely. I never felt that we were doing lesser science.

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Hughes: A common assumption in academic biology in this country used to be that if you were in industry it was because you couldn't get an academic job.

Heyneker: I never looked at it that way. First of all, I was not looking for a job here.

Hughes: Is there something different about the relationship between universities and industry in Holland?

Heyneker: No, I don't think so. I understand the concept not to be contaminated by industry, to do science for science's sake. At the same time I found—and I have not changed my mind here—that I was doing science for science's sake, and who are the academicians to say what they are doing is right and what I'm doing or what applied people are doing is wrong. Who is laying out the rules? Look, if they think their way, I have just as much right to think my way.

Hughes: So you got on with your science.

Heyneker: I got on with my science. That's exactly what I wanted to do. And I think I was quite a bit more productive than a lot of those so-called pure scientists who were wasting their time.

Heyneker's Detachment from Recombinant DNA Politics and Enthusiasm for the Science

Hughes: Were you aware that the higher-ups were dealing with political issues? One example is the pBR322 issue—Axel Ullrich was involved in this—in which an uncertified plasmid was used in cloning the rat insulin gene.

Heyneker: Yes, but that has nothing to do with pure science.

Hughes: No, the point I'm making here is that you, Herb Heyneker, because of your money from industry, are getting on with your science, and you're not distinguishing between Herb Heyneker the postdoc and Herb Heyneker the recipient of Genentech money. The academic hierarchy at UCSF had to deal with much more than science—the biohazard issue and then commercialization. How much did all this affect you?

Heyneker: [pause] Not very much, I think. [laughter] The issue of Axel Ullrich using pBR322, yes or no, you should discuss with him.[2]

PBR322 was a necessary tool to prove in the case of Axel Ullrich that he had indeed his rat insulin clone. He was doing very nice, pretty basic research, by cloning cDNAs coding for insulin. But you had to put those clones somewhere. The vector which was

2. As of Januay 2004, an oral history is in progress with Dr. Ullrich.

developed by Paco Bolivar, pBR322, was much better suited for cloning than the earlier vectors. But Axel could have done his work in pMB9 which was approved for P3 use, if I recall correctly. He could have used that as well as pBR322, but it was a pain in the butt. You could not do the same sort of positive-negative selection you can do with pBR322. I never felt that this was a big issue. It was basically the same plasmid, the same original vector.

Hughes: But other people did care, not because of the science but because of the political issue. I surmise that because you were fascinated by the science, and somewhat because of your postdoc status, you were just getting on with the science while the politics was whirling around you, and you were looking at your gels.

Heyneker: Exactly, absolutely. I was probably only very partially aware of the true politics going on at higher levels, as was also true of Axel Ullrich and Peter Seeburg. We were all postdocs. But we were definitely aware that we were on to something. It was the most exciting time I have ever had. Those two years at UCSF were probably the most exciting years because it was so novel. It was exactly as you say: here is something which is very basic coming together with something which is applied.

Hughes: Is that the essence of what made it exciting?

Heyneker: I think for me it is. The most exciting moment was when we demonstrated that we could immortalize synthetic DNA, and it becomes part of a plasmid, becomes part of a biological system. It was the first proof that you could manipulate on the genetic level with huge consequences.

Hughes: Were you sharing this enthusiasm with the other postdocs? Particularly with Seeburg and Ullrich?

Heyneker: Oh, yes. We had a lot of lunches together.

Hughes: What about the wild parties?

Heyneker: Wild parties!? I've forgotten about those, of course. No, I went always home to Burlingame.

We were young, and when you are successful, it helps enormously with your whole state of mind. It helps with your confidence; it helps with the publications you write; it helps with your future, with your career. So it really was a very positive time from that point of view. Somatostatin was the start of a new era.

Achievement Through Joint Effort

Hughes: And also the start of a new company. Have we finished discussing the UCSF period? What more would you like to say?

Heyneker: There was a lot going on at UCSF where I only played a small role. I hope in this discussion that we paint a picture that this was a joint effort—that people like Paco Bolivar, Herb Boyer, Mary Betlach all played a role in making this successful. Also, I think it is fantastic that so many postdocs from so many different places came all at the same time to the same place and probably for the same reason, namely that San Francisco was such a fascinating city. I would not be surprised also if Axel Ullrich and Peter Seeburg came here because of the magic of this place on earth. And that paid off. It is wonderful that I could collaborate with them—very smart people. And we were all the same level, so it was not that I had to go up or down. Here we were all in the same predicament, therefore we could discuss our work very openly. We couldn't care what the politics were behind it—we liked what we were doing, and we made great progress, and we shared with each other. They were aware where we stood with the synthetic DNA approach, and I knew what they were doing with the cDNA approach. I think we realized that there was validity to both approaches. We were at the threshold that all of a sudden we could manipulate bacteria, and we knew how we wanted to do it, and medical application was very important for us.

IV SCIENTIST AT GENENTECH, 1978-1984

The Somatostatin Project at Genentech

Spur to Commercial Application

[Interview 4: April 17, 2002]##

Hughes: Last time, we talked about somatostatin mainly in the context of the UCSF work. So today I thought we'd focus our attention on the Genentech part of that story, of course all related. You mentioned in session one that the somatostatin work spurred other scientific groups to consider the practical application of the new genetic technologies. Were you thinking of any specific groups when you said that?

Heyneker: No, I meant it in general. This practical application of recombinant DNA technology must have been appealing to a set of scientists. It turned out to be true that there was a large number of people who started out as pure academics who after they did this type of research decided that a little more applied research was very valuable and interesting and exciting as well. Currently, the lines between academic research and applied research are blurred. Pure research investigations have quite often a practical aspect to them. So I meant the remark in general, but a few early groups come to mind. For instance, the group led by Wally Gilbert at Harvard was of course a group we viewed as quite competitive. Also, the group of Howard Goodman in the same building at UCSF was, to a certain extent, competitive with our efforts because they also wanted to start their cloning and expression based on the cDNA approach, as Wally Gilbert did, while our approach was based on synthetic DNA.

Hughes: Both quickly become associated with biotech. Gilbert becomes a founder of a company.

Heyneker: Of Biogen.

Hughes: Yes. And Goodman in 1981 became subsidized at Massachusetts General by Hoechst.

Heyneker: Correct. He decided to move into the plant area. Goodman got his association a little bit later in the process, not as early as Wally Gilbert and Biogen and Herb Boyer's Genentech.

Hughes: Were you aware at the time that both Goodman and Rutter were approached to become part of Genentech?

Heyneker: I became aware of that. I'm not certain I was aware while I was a postdoc in Herb Boyer's lab. It might have become obvious a little later.

Hughes: There was a lot going on at that time.

Eli Lilly & Co.

Recombinant DNA Technology Applied to Human Insulin Production

Hughes: Now let's talk about somatostatin and Genentech. Scientifically, the research was a proof of principle, but what implications did the fact that somatostatin could be expressed in bacteria have in terms of the business and investment communities?

Heyneker: [pause] I think it was a very profound influence. The fact that we could demonstrate that it was possible to produce a potentially valuable substance in bacteria and therefore have a basically limitless source of that material was absolutely of great interest to the business community and to the pharmaceuticals community. Very quickly it changed the direction Eli Lilly took with their view of producing insulin and changing the production from porcine-derived material to *E. coli*-derived material. Eli Lilly saw very early on that this technology had a big impact on their insulin business, especially since they were aware of a growing population of diabetics, both Type 1 and Type 2. Therefore, a rapid increase in the amount of insulin was needed, and porcine pancreases might become a limiting factor. To have a more abundant supply through recombinant DNA technology was very appealing to them, but also to politicians who realized that in a graying population more and more insulin is needed, and to have an alternative source is something that was very important from a public health point of view.

Lilly Contracts with Competing Research Groups

Hughes: Was Lilly a forward-looking company watching for any new technology, or did they see Genentech as about to make a product that they were already selling using a new and exciting technology?

Heyneker: Lilly was placing their bets not just on Genentech. Eli Lilly was placing their bets on recombinant DNA technology to solve their problem of producing sufficient amounts of

insulin. So they placed a bet also on the Wally Gilbert approach, and they placed a bet on the UC approach—Axel Ullrich's. They had a contract, if I recall correctly, with UCSF to try to make insulin in bacteria.

Hughes: Using the cDNA approach.

Heyneker: Right. So they placed their bets at different places. So from that point of view, they were definitely forward thinking, realizing that this technology opened the door.

Hughes: Was it the insulin that attracted Lilly? Or were they looking for new technologies to make drugs of any kind?

Heyneker: I think it was the insulin that attracted them in the first place because they had to defend their market. They were the leaders in the insulin field, especially in the United States, and to a certain extent in Europe as well where they share the market with Novo Nordisk. From a defensive point of view, it was already important for Lilly to be aware of new developments in this area. Secondly, insulin is a very small polypeptide-like drug, and people might have felt that it was a more doable process than trying to express in bacteria an entire big protein like tPA.

Uncertainty About Expression of Foreign Genes in Bacteria

Heyneker: Let me remind you that there were a lot of unknowns with regard to expression of foreign genes. A lot of skeptics worried that the codon usage in eukaryotes was completely different than in prokaryotes, and that nature had devised some other barriers to keep the prokaryotic world from interacting with the eukaryotic world. Twenty-five years later, using all the advantages of recombinant DNA technology, we now know that there are interactions between prokaryotes and eukaryotes and that the division line is not as sharp as people thought.

Hughes: You mean interactions in nature?

Heyneker: In nature, yes, absolutely. Nature is trying to use every trick in the book to renew and to find new opportunities for life. So we currently look at it differently than in those days. It's important to keep that in mind.

So there were a lot of people saying that it will never work. When we showed the fusion-product approach to somatostatin, it was a step forward, a step in the right direction. Especially by using synthetic DNA where we on purpose used codons which were abundantly used in bacteria, you could say, using this approach we still try to abide by the rules for prokaryotic organisms like bacteria. With cDNA, you were already one step further because you did not have the flexibility to change codons. With the cDNA approach, you use codons as they are being used in a eukaryotic organism.

Perhaps I digress a little, but I'm coming back to Eli Lilly. They didn't know what would work exactly, but they absolutely wanted to be there on time, and I wouldn't be surprised if after producing recombinant insulin that they of course would become interested in

other protein-like therapeutics. I can imagine, and as a matter of fact that's the way it happened, when you invest a lot in recombinant DNA technologies early on, that you become interested in it, you understand the process, and that you want to play in other recombinant DNA products is very logical. But it is a sequential process; I don't think Lilly had the vision immediately that they were going to become a true competitor of Genentech. Although they tried later, of course.

Hughes: You said last time that you didn't have a problem believing that human proteins could be expressed in bacteria. So why didn't you buy into the dogma that there was some sort of invisible barrier between the prokaryote and the eukaryote?

Heyneker: Well, I didn't have to because we were focusing on synthetic DNA. Right? But later during my career at Genentech, we were very busy trying to understand these issues better. For instance, when we tried to express alpha-interferon in bacteria, it was a great disappointment. It was incredibly difficult, and in the beginning we could not produce this molecule in bacteria, and we were very worried about it. All of a sudden, things we didn't know—codon usage and barriers between prokaryotes and eukaryotes, secondary structure, tertiary structure of RNA; you name it—lots of things became important, and we needed to sort them out.

Communicating the Success with Somatostatin

Hughes: What would you like to say about the announcement and publication of the work on somatostatin?

Heyneker: Well, [pause] what I do recall is that it was an incredibly exciting time. I felt on top of the world. I felt incredibly grateful and lucky to be part of the team that was the first to make the first step for the manipulation of bacteria in such a way that you can make products of interest. Yes, I felt it was amazing. It opened up so many avenues; you could envision so many things you could do all of a sudden.

Hughes: Mainly in the applied area?

Heyneker: Yes, I always enjoyed the applied area. As of today, the fact that we worked on human growth hormone and tPA, et cetera, et cetera, and that people got treated with these drugs is for me very gratifying.

When this work was finally really done and a paper came out, it was more or less at the end of my second year at UCSF, and I had to go back to Europe, with mixed feelings, because I felt I was currently part of something of historic proportions, and I wanted to continue to be associated with this research.

Hughes: The somatostatin paper came out—

Heyneker: It was 1977 that the paper came out. I think it was around August that the paper was published, or even a little bit later,[1] because I went on a tour in the United States to talk about this work.

The somatostatin team, City of Hope Medical Center, 1977. Back (l to r): Arthur Riggs, Herbert Boyer, Keiichi Itakura, Roberto Crea. Front (l to r): unidentified, Herbert Heyneker, Paco Bolivar, Leonore Balce Directo, Tadaaki Hirose.

photo courtesy of Roberto Crea

Hughes: Somebody mentioned that you had given a talk on somatostatin before the paper came out.

Heyneker: Well, that's possible. At UCSF I gave a talk on it as well.

Hughes: Well, there was a little controversy when it came out, as you probably remember. The ethics of science at that time was that a scientific discovery should not be announced before the paper describing it was published. The news conference was at the end of the year.

Heyneker: Yes, prior to that press conference, I talked about it at UCSF. UCSF was my alma mater for those two years, and I felt that you are absolutely able to discuss your work inside your university prior to publication. I never saw that as a breach.

Hughes: The fact that you had discussed it in an academic setting was a plus in terms of the City of Hope-Genentech announcement; this work had been presented in a scientific setting before the press conference.

Heyneker: What really is the issue is not that you talk about it, but that you make a true press release and give the pitch to the entire outside world through the press, without the scientific press having it announced first or concomitantly. And that is still a rule which holds.

I scheduled a series of seminars from the West Coast to the East Coast on my way back home to the University of Leiden. My time was up, and I had made a commitment to go back to Holland because they had kept a place open for me to start my lab at the university.

Hughes: You implied that you felt two-minded about going home.

Heyneker: Of course—I didn't know what to expect in Holland.

Heyneker's Ties with Commercial Production of Research Enzymes

Heyneker: The timing of the somatostatin work was good from the point of view that it was all done before my second year was over. I used those last few months in an interesting way. Before going on this road trip, I spent a week at a very small startup company called Life Technologies. That company's goals and objectives were to provide enzymes to the recombinant DNA research community, like restriction enzymes, ligase, polymerase, and so on. So they saw an opportunity to commercialize those enzymes. Before Life Technologies was started, scientists had a bartering relationship with other scientists. You acquired restriction enzymes through the mail from your colleagues, or you exchanged with other people, or you had to make your battery of restriction enzymes yourself. It was a lot of work, and by disseminating them, you could speed up recombinant DNA research dramatically.

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1. See #15 on Heyneker's bibliography. The paper was published on December 9, 1977.

So Life Technologies had a good vision: They wanted to provide these products to the research community so that you no longer had to barter, but you could just buy them straight out. They would fill out a catalogue of products and add to it. Now, of course I had a lot of experience with enzyme purification, including ligase and polymerase. Pat Greene and I had worked out a robust purification system for a whole slew of different restriction enzymes, and so it became a very standard procedure. So I spent some time at Life Technologies. It was called BRL in the beginning, Bethesda Research Labs. It later changed its name to Life Technologies. I visited them, I would say, sometime in late August, early September [1977]. It was incredibly hot that week, and I basically taught them how to make DNA ligase.

Hughes: Had you contacted them?

Heyneker: No, they contacted me. As a postdoc, I could always use a little extra money.

Hughes: Of course, and how did they know of you?

Heyneker: Well, there were not that many labs in the nation which were doing this sort of work. Probably they asked around.

Hughes: Did BRL have a corner on the market for a number of years?

Heyneker: They had sort of a corner on the market; I think they were mildly successful, but they got into financial problems, and it was Gibco which rescued them. Of any company, it was surprising that they came to the rescue. The name was changed to Life Technologies. In the meantime there was competition. New England Biolabs started also a catalogue of restriction enzymes. They are still around and very much focused on the same initial mission.

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Heyneker: Life Technologies was acquired by Invitrogen. They really provide much broader service for life sciences researchers, including cell biologists, and so on. Together, they have a very broad portfolio of products.

Hughes: What about Genex, which was an early biotechnology company? Were they doing that kind of thing?

Heyneker: No. Genex wanted to commercialize the technology, not provide service. There were other people who could do it. They were more like competition to Genentech, to a certain extent. They were more focused on industrial products. [J.] Leslie Glick was the founder.

Heyneker's Speaking Tour

Hughes: BRL was your endpoint as you were wending your way across the continent?

Heyneker: Well, this experience with BRL came first. I went back to the lab [at UCSF] to wind things up, and then, I think in October, we rented a Volkswagen camper bus, and my family and I toured for two weeks through the western states, ending up in Albuquerque. Then the bus was driven back by somebody else, and I started my [speaking] tour. I started first in Athens, Georgia, because my good friend Rich Meagher, who was also a postdoc at Herb Boyer's lab, became assistant professor at the University of Georgia in Athens. He invited me to give a talk.

Hughes: What about your family?

Heyneker: They probably amused themselves a little bit. Don't forget my oldest son Marc was five, and Thys was two years old.

Hughes: And Phil was not born.

Heyneker: Right.

Hughes: How did people receive your talk on somatostatin?

Heyneker: I think they shared my enthusiasm. A seminar where there is a very clear line of research, a very clear goal and outcome, and a spectacular outcome is a pretty easy seminar to give. It was a very exciting seminar to give. I was looking forward to it.

Hughes: In addition to talking about the exciting science, were you also talking about the practical implications?

Heyneker: Of course. I can't recall exactly what happened, but absolutely the audience of course thinks forward and asks questions, and in that regard as well.

Hughes: What happened after that?

Heyneker: From Athens we flew to Washington, and I gave a seminar in Phil Leder's lab, who was then at the NIH in Bethesda.

Hughes: How was that set up?

Heyneker: Why did I go there? I called them, and I said that I would like to give a seminar. Postdocs also do that, so if they are on a tour, especially if you have something new to present, a talk's not too difficult to arrange. The plane was late, and I had to rent a car, and I didn't know where to go; I think I arrived ten minutes late. By the time I started my seminar—it was really a tight schedule, let me put it that way. From there I went to Harvard and gave the same seminar to Wally Gilbert's group.

Hughes: He must have been all ears.

Heyneker: Absolutely. He's a great guy.

Hughes: Was Biogen a sparkle in his eye yet?

Heyneker: No, I don't think Biogen was a firm yet.

Hughes: Biogen was founded in 1978.

Heyneker: This was still '77.

Hughes: Who knows? You may have planted some seeds.

Heyneker: Oh, very possible.

Hughes: Do you remember anything specific about that seminar at Harvard?

Heyneker: [pause] Well, not in great detail, except I felt that I was going into the lion's den, and I was expecting some pointed questions. But, yes, I think it went okay. They were very supportive. I never felt that Wally gave me a hard time.

I think I went to a few more places, but the only other place I recall was Cold Spring Harbor, which is by the way an interesting story, and I should tell it here probably. I think that I asked Jim Watson if I could give a seminar there, so he was my official host. I went to his office, and we talked a little bit, and then he said, "Well, Herb, I'm sorry, but I won't be at the seminar because I'm invited out by a very beautiful young lady for lunch. What would you do if you had the choice—to go to a seminar or go to lunch?" So I had to say that probably I would do the same. And he said, "After all, I know what you're going to talk about; I know what the outcome is, and what it's all about." And he was right; I don't think there was anything particularly novel to learn, but I was definitely a little bit surprised as a young postdoc to hear that. So somebody else took the honors or whatever to introduce me at the seminar.

Hughes: Were you a little disappointed?

Heyneker: No, I really wasn't. I was totally excited that I was allowed to give the seminar there; I was totally excited that I had a chance to exchange a few words with Watson. No, no, far from it.

Hughes: Was that your last stop?

Heyneker: Yes, that was the last stop, and then from there the family flew back to Holland. That whole trip took us around three weeks. It was a terrific time—a great time to enjoy nature. It was in October with hardly anybody in the parks. It was just spectacular. And it was an outstanding time to share that information with top labs in the United States, so I felt it was just a glorious end of my postdoc years.

Hughes: Was Boyer also talking it up?

Heyneker: Well, I'm not sure that we were talking it up. We were talking about it. [laughs]

Hughes: Well, all right. Talking about it. [laughter]

Heyneker: Yes. Probably.

Hughes: How fast was the word getting out? How much was known before the paper came out in December?

Heyneker: I think that the day the paper came out, I was in Phil Leder's lab. So thereafter, it was not as novel anymore. This is what I recall—twenty-five years later or whatever. [tape interruption]

Return to Holland

Charles Weissmann's Invitation to Visit His Geneva Laboratory

Hughes: You have a story about interacting with the Weissmann lab.

Heyneker: Yes. After returning to Holland and starting at the University of Leiden, I received an invitation from Charles Weissmann to visit his lab in Zurich with the goal to help to teach them some of the recombinant DNA technologies. Of course I was very flattered, and I accepted the invitation, and for almost two weeks I was in his lab. We started a project, and I have forgotten even what it was, but mainly it was to teach them techniques the way we did reactions, the way we analyzed the results, and I got to know him quite a bit better.

Hughes: You had met before?

Heyneker: No, I was aware who he was, but we never met before. Interestingly enough, he was running his lab in a very old-fashioned way, and the students called him Herr Doktor Weissmann, and he held his seminars preferably on Saturday morning to make sure that people were not—

Hughes: Lying in bed.

Heyneker: Exactly. Were definitely dedicated and devoted to science.

Hughes: This was not necessarily the Swiss way?

Heyneker: That was probably the Swiss way. It was definitely a very formal situation, something which even in 1977 was not going on in the United States. However, if you were a postdoc from the United States—and he also did a postdoc in the United States—then the rules were changed. Then you belong to a certain club, so I could talk to him, I could mention "Charles" instead of "Doktor Weissmann," and he called me Herbert. So that really helped. I think we really had a very good relationship. The work went well. I think the transfer of technology was successful.

Hughes: Was he actually at the bench?

Heyneker: He was no longer at the bench, but he was so close that he knew exactly what was going on. He was still analyzing every gel.

Hughes: Tell me your impressions of him as a personality.

Heyneker: I was very impressed, being a young postdoc. He's a very well-established, very smart person. In those days he was close to the lab, really making good observations and having a very efficient way in going forward. I think a great experimenter, working on important projects.

One day I was invited to his home, which was more like a castle. He's pretty well off. When I arrived I was given one of those—how do you call those little—he was from a Jewish background.

Hughes: Yarmulkes.

Heyneker: I was given a yarmulke, and then we had a nice dinner, and we played chess in the evening, and I still remember it was a delightful chess game. It was very challenging. He won in the end, but I gave him enough of a match that he enjoyed it. I was very impressed that Weissmann invited me to bring him up to speed very quickly in this new field. He was the only professor who invited me.

Teaching Pieter Pouwels Recombinant Technology

Heyneker: My former boss and promoter in the Netherlands, Pieter Pouwels, is also a very forward-thinking scientist, and he definitely took lessons also, wanted to learn the new technology, and made sure that he came to my lab in Leiden on a day-to-day basis for up to a month to really understand the ins and outs of the technology. Then he took it back to TNO, and I loved that. It was great that he took the time and effort to learn it from me, and I was very glad that I could give something back, in a way.

Hughes: Yes. And it tells a lot about him that he would take instruction from a former student.

Heyneker: Oh, absolutely. We became very good friends. We were always quite close, but something like this cements the relationship.

Effects of the Recombinant DNA Debate in Holland

Heyneker: There was one other person who came to Holland, and that was Mattie Servas. He came from Helsinki, Finland, and he wanted to do some work on *Bacillus*. He came to learn this technology and to do some experiments together, cloning a gene from *Bacillus subtilis* in *E. coli*. At least that was the premise.

Hughes: Had you known him?

Heyneker: No, I didn't know him; he approached me. But by the time he arrived in Holland—I had been back for half a year—recombinant DNA technology was viewed in Holland as potentially dangerous, and there was a big movement to stop this type of research–certainly till we would know more about the implications.

Hughes: Stop it across the board?

Heyneker: Well, they never said stop it across the board, but the official line from the Ministry of Education was to be cautious and avoid if possible recombinant DNA technologies. It was almost a moratorium. It was not forbidden, but it was strongly encouraged not to engage in these types of technologies.

Hughes: Could the ministry control the purse strings?

Heyneker: They could to a certain extent because, let's say, an experiment I wanted to do with Mattie Servas needed the approval of an oversight committee, like the NIH committee.

Hughes: The NIH Recombinant DNA Committee?

Heyneker: Yes. In Holland we had also some sort of an ad hoc committee, and there were clear objections to this research. Imagine being concerned about cloning from one bacterium into another! So Mattie Servas had to go home. I think he stayed for a few days, and I taught him a few basic things about cloning. I sent him on his merry way with some ligase and restriction enzymes, saying, "Look, continue your work in Finland if you're allowed to."

Hughes: And was he?

Heyneker: I don't know. I was in contact with him now and then, but unfortunately this collaboration was aborted.

Heyneker's Decision to Return to the United States

Wish to Remain at the Forefront of Recombinant Technology

Heyneker: The reason why I give this episode quite a bit of attention is that it really became clear to me that I didn't want to stay in the Netherlands under those conditions. I was at the forefront of this technology in the United States, and to stop this line of research, knowing that my colleagues and other researchers would continue and move on from where I left off, was difficult to swallow.

Hughes: [laughs] No competitive genes in your makeup!

Heyneker: Well, there were clearly competitive genes. But it was something which I had at my fingers; I had done it for two years; I knew exactly what to do.

Hughes: That was an inappropriate remark on my part.

Heyneker: Well, in those days I was competitive. All postdocs were competitive. It was very important to be first.

Hughes: You also had had an important part in founding this technology. You had a right to be concerned about remaining part of it.

Heyneker: Absolutely—I loved it—absolutely. Although I want to say here again: It was not me alone; I was part of the team which collectively moved this technology forward in a rapid fashion.

A Standing Invitation to Join Genentech

Heyneker: So this episode helped me enormously to make the decision to return to the United States.

Hughes: Had that been a possibility all along?

Heyneker: It was a possibility all along. When I left, I had a standing invitation from Genentech to go back and be part of the founding team.

Hughes: Who specifically issued the invitation?

Heyneker: Bob Swanson and Herb Boyer.

Hughes: And your response at that point was, "I have to go back to Holland"?

Heyneker: That was my response. I had to go back because Holland paid for my first year, and it was on the premise that I would return to Holland and disseminate the technology I learned in the United States. Here's where the conflict is: I was more than willing to do that, but I was not allowed to do that. So that was a contradiction. I tried to point out to the funding agency that I wanted to disseminate the technology, but I couldn't. But that was not enough of an argument, so then I offered, "Look, in that case I will see if Genentech is willing to pay my stipend"—to get out from under the obligation.

Hughes: Was there anybody at the University of Leiden who was trying to help you with all this? After all, you were a young person relatively low in the academic hierarchy.

Heyneker: Well, there were two professors in the biochemistry institute with whom I was close, and one was Professor Rorsch. He was my promoter, and he understood my predicament. He was very much helping me and understanding the situation. The other was Professor Leendert Bosch who is a very nice person who did not want to see me leave and did not agree that I would go back to the United States. And so they made sort of a counterbalance, and I understand both points of view. So in the end I had to make the decision myself.

More on the Recombinant DNA Issue in Holland

Hughes: There was nobody in a position to argue with the ministry imposing this moratorium? People around you couldn't manipulate the political situation in terms of recombinant DNA?

Heyneker: There were definitely advocates of the technology, and there were definitely people who wanted to stop it, so there was a big discussion going on. But in the meantime, while the discussion was going on, that type of research was really discouraged.

Hughes: So it wasn't like the research moratorium in the United States which excluded only certain types of experiments. In the U.S., all along, there were certain types of experiments using recombinant DNA technology that could continue.

Heyneker: Correct, under the proper conditions.

Hughes: But in Holland there was no leeway to do certain types of recombinant DNA experiments?

Heyneker: It was a more blanket statement: Let's sort this out first. Again, there were no rules and regulations. It was sort of a guideline and a blanket statement to be cautious and try to avoid this type of research for the time being. My reaction to that was, well, okay, then for the time being I'm going back to the United States, and then we'll see.

Hughes: Were you the only one in Holland at that time who knew this technology?

Heyneker: At that time, yes, I would say, although it doesn't take long for others to catch on. You're never alone for a long time, and that's good.

Heyneker's Confidence in the Commercial Viability of Recombinant DNA

Heyneker: The one person I had to discuss this with was my wife Pauline, because it really meant that we would go back to the United States for a longer period of time. But she appreciated the opportunity I had at Genentech, and I think she was very willing to return.

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Hughes: Did she understand the risk that you were taking?

Heyneker: Of going back and being paid by this fledgling company called Genentech?

Hughes: Yes.

Heyneker: I was absolutely convinced that it would work. I was naive enough that I thought that this is a unique opportunity. I didn't see serious technical risk. That's a good question, and if I had to do it again, with the knowledge I have now about starting a company and being

successful with a company, I probably would have hesitated a little bit longer. On the other hand, it was truly unique, novel technology. It was a great opportunity, and I would have been very sad if I had not taken this opportunity. I would read about it later and know that other people have been successful. It's something I wanted to be part of. So no regrets, of course.

Swanson and Boyer Reinforce Their Offer to Heyneker

Hughes: Don't I remember that Bob and Herb came to Holland to persuade you to join Genentech?

Heyneker: Absolutely.

Hughes: Well, tell me about that.

Heyneker: Well, that was a reinforcement that indeed Genentech had this standing invitation. I think Bob and Herb had to go to Denmark, and they swung by Holland to take me to a very nice restaurant in Amsterdam and to lay it out again, what part I could play at Genentech.

Hughes: Do you remember when that was exactly?

Heyneker: I think it was in February of 1978.

Hughes: So that means that the work on insulin was beginning to take off—

Heyneker: Correct, without me! [laughs]

Hughes: [laughs] Yes, without you!

Heyneker: After that dinner I gave the founders, Herb Boyer and Bob Swanson, a strong indication that I wanted to come back because I had seen already enough that this recombinant DNA technology in Holland was on hold. But there was one problem. Pauline was pregnant with Philip, and we did not want to leave the country before he was born and old enough to travel.

Hughes: You wanted him to have Dutch citizenship?

Heyneker: Well, possibly. It was more that Pauline wanted the support of her Dutch friends and family in the process of delivering the baby. And I can understand that; I had zero problems with it. So the last four months we all knew that we were going back to the States and that the moment was when Philip would be old enough to travel. So we left the country when he was three weeks old.

Research with Pieter Pouwels and Frank Graham

Hughes: What did the delay mean for your work?

Heyneker: For the last four months?

Hughes: Yes.

Heyneker: I continued to work closely with Pouwels. We had a publication together.[2] That was a time in recombinant DNA research where we did not go from one species to another species. It was recombinant DNA technology from *E. coli* to *E. coli.* So it was in the same species. Good for learning, but not truly exciting. So that went on, and that was all fine. I enjoyed myself. I gave seminars. Also I started a collaboration with Frank Graham. He was a postdoc/scientist in the lab of Alex van der Eb, who was quite the world authority on adenovirus. They did some very early pioneering work on transformation in eukaryotic cells, and I had some technology in my lab which could help them to answer some of their scientific questions, so that definitely kept me occupied. It was a nice piece of work on their part. So time flew.

Interim Visit to the United States, May 1978

Tom Perkins's Party

Heyneker: I went back to the United States in May for a couple of weeks, and the purpose was that I was going to look for a house so that when we would arrive in the States we would have a place to live. But the real reason was that I felt I had to go to Genentech to talk things through and to get the employment process going. While I was there, there was a panic, and you must have heard about this panic from Goeddel and others. Namely, that Genentech people like Dennis Kleid and Dave Goeddel were cloning the A-chain and the B-chain of insulin, and they were quite successful in doing so. We were invited to a reception/dinner at the home of Tom Perkins who was one of the principals in the famous venture capital firm Kleiner & Perkins. We told them that we had cloned the A-chain and the B-chain and that the insulin project was making fantastic progress. However, we had just learned a few days prior that there was a mistake, I think in the B-chain, but we were too chicken to tell that to Tom Perkins, because it would be disappointing. So we went to the party as if things were hunky-dory.

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2. Heyneker bibliography #22.

Emergency Visit to City of Hope

Heyneker: But immediately thereafter Dave Goeddel and I went to the City of Hope to reclone the B-chain. That was an absolutely fantastic experience, because here I was with Dave Goeddel whom I didn't know. He was a postdoc hired by Dennis Kleid. All of a sudden, fresh out of Holland, I had to go to City of Hope and reclone the B-chain. We worked so well together. He understood exactly what I wanted to do, and I understood quite well what he wanted to do, so we took turns sleeping, to speed up things. When we had to label the DNA fragments, we were so much in a hurry that we exposed an x-ray film only for as short a time as possible and looked at an angle at the film so that we better could see a slightly darker position—everything to be as fast as possible. We had a bunch of clones within a week or five days. And we took them home, they were sequenced, and we were successful in getting the right B-chain. [laughs] I don't think we ever told Tom Perkins, or only perhaps years later, that there was a little glitch. The experience was fantastic, very exciting—how efficient you can be. It really helped me to build a relationship with Dave Goeddel right away.

Hughes: Was the pressure coming from what you were imagining Tom Perkins was thinking?

Heyneker: Well, it was more the pressure that we told him that we had it and to then later say, well, no, we don't have it. It doesn't show well. It's a little bit flaky.

Hughes: You had to correct it.

Heyneker: Exactly. We were confident that we could correct it.

Hughes: It's not obvious to me that you had any obligation to help. You were in the country to look for a house.

Heyneker: Yes, but I had become part of Genentech, right? They knew that I had signed up and that I would start end of August, beginning of September. So I was part of the team. I wanted to make sure that they realized that I was part of the team, so that the people who were hired early on, like Dave Goeddel and Dennis Kleid, knew me.

Heyneker and Dennis Kleid: Mutual Encouragement to Join Genentech

Heyneker: By the way, Dennis Kleid and I knew each other from years back. I think he gave a seminar in Holland, and I hosted the seminar—something like that. I can't recall exactly how we got to know each other.

Hughes: Didn't you have something to do with Kleid joining Genentech?

Heyneker: Yes, absolutely.

Hughes: And of course Kleid brought Goeddel.

Heyneker: Yes. Kleid and I exchanged letters, Dennis telling me that he would come if I would come, which put more pressure on me. I would say, "Okay, if I come, I want to make sure you come too." We encouraged each other to join Genentech.

Hughes: What were your first impressions of Dave Goeddel? Other than that he worked fast.

Heyneker: Yes, and very efficiently. He was my type of guy because I only had to explain something once, and he let me in a way lead the project. He probably understood that I had more experience at that time than he had. But he was so good at picking things up that by the end of the week we were basically doing the same thing. This was a very exciting experience.

Hughes: Did that compatible method of working together continue into later projects?

Heyneker: Oh, I think so. I always had a good rapport with Dave as far as I remember, although at one point in time he led a lab, and I had another lab, so I did different things than he did.

Hughes: How did the house-hunting go?

Heyneker: It didn't go. In retrospect, Pauline should have been very much involved with the house-hunting. After all, she was going to raise the kids there, so for her it was more important to have a good home than it was for me. I think house-hunting was perhaps an excuse to go to the United States and say something like this.

Arrival in the United States

Mixed Emotions About Leaving Holland

Heyneker: At the end of August we made the move back to the United States.

Hughes: Did you have any regrets about leaving your homeland?

Heyneker: Well, it was not that easy, especially with family. I hadn't seen my parents for two years while I was at UCSF—we did not come back in the meantime—so the reunion was great. My parents were getting a little older, also Pauline's parents and family. I have two sisters; Pauline has a brother. So life in Holland was good. We didn't leave Holland because we didn't like it there; we left because I had this great opportunity here, and at the same time that opportunity in Holland was cut off temporarily. You can only be in one place at a time. So, yes, we realized the States were far away, and we knew that we would miss certain aspects of Holland, especially our social life, but we were excited to start our life, our family, in the United States. So we left Holland with mixed feelings.

Arrival in California

Heyneker: We arrived at the airport, and we went straight to the Hilton at the airport where Genentech had rented a couple of rooms for us, because by now our family counted five members, Pauline and I and three kids. The Hilton had a little swimming pool and was very close to Genentech. Bob Swanson made South San Francisco his base which I think was probably a very good decision. From the Hilton to South San Francisco was a ten-minute endeavor. It was also, let's say, ten minutes from the Burlingame area, and as you may recall, most of our postdoctoral time we lived in Burlingame. So Pauline knew people there, was comfortable there, and we decided to look in the Burlingame area, which is a very good family area, for housing, which we found. I would say two weeks later we moved into a wonderful house in Burlingame, and that's where we started.

The New Genentech Facility in South San Francisco

Hughes: You had not at that point spent very much time at Oyster Point in the new labs. I guess by that time they would have been together.

Heyneker: Yes, I think they were together. But when I was there in May, we did not occupy the location in South San Francisco yet. I think Bob was looking at other opportunities as well. Brisbane was another possibility. But in the end he settled for South San Francisco. When I came back at the end of August, yes, there was a lab up and running, and I was ready to roll.

Hughes: Three other scientists were there at that point? By then Dan Yansura was there.

Heyneker: Yes, Dan Yansura was hired. Shortly thereafter we hired Liz McCloud who later married and became Liz Yelverton.

Hughes: Who was a scientist?

Heyneker: Technician. Very smart. She got her Ph.D. later in life.

Heyneker Urges UCSF Postdocs to Join Genentech

Heyneker: We were working hard to try to convince Peter Seeburg and Axel Ullrich and John Shine, all postdocs from the Goodman lab, to join us.

Hughes: Did you have a major role because at Genentech you knew them best?

Heyneker: Absolutely; I had a significant role. I still remember the first week after my arrival we had these meetings in the courtyard around the swimming pool at the Airport Hilton where we discussed all the pros—there were no cons—of joining Genentech.

Hughes: [laughs] In your mind, but not in theirs.

Heyneker: Of course. I was trying my hardest to convince them that it would be a fantastic opportunity.

Hughes: What was their main stumbling block?

Heyneker: I don't know exactly, but I can imagine that it was to give up academic life and become part of a company. That was a very novel concept. I think they had the feeling that they'd give up a lot by trading in their academic life. Also it meant that they wouldn't go back to their home country. By the end of the day, I think Axel Ullrich and Peter Seeburg both accepted, but John Shine did not join. I think he was a consultant for a while, but he moved back to Australia. It was very unfortunate. Great guy. I wish that he would have joined. He would have made a tremendous contribution. But I was delighted that Peter Seeburg and Axel Ullrich wanted to join.

Hughes: Which they didn't do right away.

Heyneker: Correct. But we had the understanding that they would join. I think they wanted to finish work at UCSF.

Heyneker Becomes Genentech's First Director of Molecular Biology

Hughes: Where was the insulin project when you came back in the fall? Presumably you jumped right into the project again.

Heyneker: I think we started to work on the next project, human growth hormone.

Hughes: Oh, already.

Heyneker: Yes, very soon after my arrival. We were already discussing the project before Peter was physically on board.

I started out as the director of molecular biology. That was a little bit of an overwhelming task for me.

Hughes: Why do you say that?

Heyneker: I didn't feel that I was in a position to direct my colleagues. We were all in the same boat, same age and so on. So I was director but—I can't recall exactly when but quite soon—we hired Giuseppe Miozzari from Stanford. After a couple of months he took over as the director of molecular biology.

Hughes: Why he rather than you?

Heyneker: Well, it was not my ambition. I wanted to be in the lab; I wanted to be hands-on.

Hughes: Being director of molecular biology required a lot of administration?

Heyneker: Exactly, and I was not looking forward to the administrative part.

Hughes: At such an early stage of the company, I would think that all the scientists would be at the bench.

Heyneker: That's correct, we were. But I think that was never my strong suit to be in charge and take on the administrative duties. As a matter of fact, it's still not my strong suit. Perhaps I should have learned better then.

Hughes: So you happily went back to the bench?

Heyneker: Oh, absolutely.

Genentech's Human Growth Hormone Project

Designing a Part Synthetic, Part Natural Gene

Hughes: Did you pick up the growth hormone project?

Heyneker: Yes, I was definitely involved also in helping with the design of the growth hormone project. We realized that this was a gene that was way too large to synthesize in its entirety by chemical means. That would have been too much work, too difficult, although now you would do this literally in a few days. Then this was impossible. So we designed the human growth hormone project in a way that part of the gene we would synthesize by chemical means and part of the gene would come from cDNA.

The reason for this design was several fold. First of all, the front part of the human growth hormone gene was made by chemical synthesis, which assured us, because we had the flexibility of what the DNA would look like, to make sure that it would be in perfect register with the lac promoter and also that it would seamlessly connect to the cDNA part. The power of synthetic DNA is its flexibility. If you started with cDNA in its entirety, to hook it up perfectly to a promoter region would be quite challenging. I was in charge of the synthetic part, so I would clone all these fragments and build up that front part of the gene while Dave Goeddel was focusing on the back part of the gene, the cDNA part of the gene.

Hughes: Well, if you were doing the DNA synthesis part, what was City of Hope doing?

Heyneker: No, I was doing the assembly part.

Hughes: Oh, I'm sorry, I thought you said—

Heyneker: Well, you're correct. What I meant was that I would do the assembly of the front part of the gene, starting with cDNA fragments.

Hughes: Which you were getting from City of Hope.

Heyneker: Correct. [pause] Although we hired pretty early on Roberto Crea from City of Hope, and we were starting our own DNA synthesis laboratory at Genentech.

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Hughes: What was City of Hope doing?

Heyneker: Well, I think it was a hand-off situation. I think that City of Hope made quite a few of the fragments for human growth hormone, and they were involved in the design of the synthetic DNA, but over time we would make our oligonucleotides in house. And when that happened exactly, you might have to refresh my memory. I don't know exactly when Roberto came on board.[3]

The Human Insulin Project

The Race to Provide Sufficient Insulin to Lilly

[Interview 5: April 23, 2002]##

Hughes: Dr. Heyneker, as we discussed off tape, we are going to tackle the insulin story. Do you remember at what stage it was when you arrived?

Heyneker: I knew by that time that the genes coding for the A-chain and the B-chain were cloned and expressed, and that the sequence was correct for human insulin. Where my recollection is less crisp is what happened thereafter. It mainly became a protein biochemistry project, namely the purification of the proteins coding for the precursor of the A-chain and the B-chain and the fusion proteins, and then activation of A-chain and B-chain with cyanogen bromide.

Hughes: Who was involved?

Heyneker: Well, I'm pretty sure that Ron Wetzel was responsible for that assay.

Hughes: You arrived at Genentech in late August 1978, right?

Heyneker: That's correct.

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3. Crea joined Genentech in the fall of 1978.

Hughes: It was about the time insulin was expressed.

Heyneker: Yes. The chronology refreshes my memory, but interestingly enough that is not what I remember as the most important accomplishment in the insulin work. What really comes to mind was the work against the clock by Ron Wetzel to produce sufficient amounts of properly recombined A-chain and B-chain to make a couple of milligrams of insulin—sufficient amounts for Eli Lilly to demonstrate biological efficacy. That was critical for us because there was a deadline, and if we couldn't meet the deadline it would really have implications for the funding of Genentech. So perhaps it was out of survival that that was a more important moment.

The Press Conference

Hughes: Going back to an earlier period, did you go to the press conference at City of Hope?

Heyneker: I can't recall. I have been to City of Hope many times, and I remember that we were always at the fountain and pictures were taken and so on.

Hughes: It was quite a dramatic affair. There was a lot of press, and the Genentech scientists and the City of Hope scientists were lined up on a stage, and there were questions from the press.

Heyneker: I probably was not there that day.

Struggling to Meet Benchmarks

Hughes: What were Lilly's expectations? What did Genentech have to produce in order to keep the funding going?

Heyneker: In those early days, those timelines might have been aggressive. Quite often—I'm speaking from experience—projects at first look extremely straightforward and doable in weeks. To get robust results—to do all the controls and so on—often takes longer than people anticipate. So I wouldn't be surprised if we had pretty aggressive timelines, which we absolutely wanted to keep. Backpedaling, especially for a young vulnerable company, is not the right thing to do. So again, I think that's why I recall that we were so anxious to meet the deadline.

Ron Wetzel and the Reconstitution of the Insulin Chains

Heyneker: Ron Wetzel did a fantastic job in doing so. The reconstitution of insulin from A-chain and B-chain was not really a proven, robust technology. It was a very difficult task to do.

Ron Wetzel was to a large extent pioneering on how to bring the A-chain and the B-chain together under conditions that they would refold together in natural form. Don't forget, nature does it quite differently. Nature makes one pro-insulin chain, and the pro-insulin, which is a significantly larger protein because it has the internal C-peptide, folds. Subsequently the C-peptide is cleaved out from the insulin by protolytic enzymes. We had to do it a more chemical way, so there were a lot of unanswered questions. People did not have the luxury to have large amounts of A-chain and B-chain floating around in two different pots and then bringing them together.

As a sideline, I think Eli Lilly did an incredible job to scale up this process to a commercially viable process. After a few years, they changed the protocol. I think they went to a mini-C protocol to produce and refold the insulin. But to scale this up and make sufficient amounts to flood the world with human insulin, so that porcine insulin is no longer needed, I think is pretty significant.

Hughes: That part of the procedure Lilly was handling totally on its own without any interaction with Genentech?

Heyneker: I don't know, but I'm pretty sure that Ron Wetzel handed over the project and explained to Lilly how he did it. Ron tried a lot of different refolding procedures before he found the most efficient one.

Hughes: Were those procedures in the literature?

Heyneker: I don't think so. There might have been some hints how it could be done, but to optimize it, I think it needed quite a bit of creativity. All the work Ron did on it of course was transferred to Lilly, and it formed the basis for them to scale it up.

Hughes: You spoke of having A-chain and B-chains in different pots. Nobody else but Genentech had A- and B-chains in different pots, did they?

Heyneker: That's correct, of course, because we synthesized the gene by chemical means. We used the same sort of strategy as for somatostatin, and it is completely artificial. Nature is not doing any of this work at all. We used nature to make the A-chain and B-chain, but then we needed chemistry to bring them together.

Hughes: It seems to me a tremendous leap of faith that by these artificial manipulations, you could indeed produce a biological molecule that retains the function that you want.

Heyneker: Well, I don't want to go that far. However, we were probably more worried that only a very small proportion of the refolded material would be biologically active so that we would have to go through a massive purification campaign to separate the biologically active material from the rest. I don't know, perhaps Eli Lilly went through such a step, but I'm pretty confident that they found a way where the majority of the material folds correctly. So yes, there was a leap of faith. Protein biochemists knew quite a few things about behavior of proteins and peptides, so it is not completely that we started from scratch. But yes, there definitely was some leap of faith.

Hughes: Do you think that Ron Wetzel was exceptionally dexterous?

Heyneker: He was a very good experimenter. I have the highest esteem for him.

Hughes: How had he been attracted to Genentech?

Heyneker: I think that Mike Ross attracted him.

The Contract with Lilly

Hughes: One of the amazing things to me in this story is that there was no contract with Eli Lilly until late August, when there was evidence that Genentech had expressed insulin. Yet it sounds from the stories that people have told me as though Swanson's recruiting efforts were floated on the assumption that there was a contract in place, not only with Eli Lilly but also with Kabi. What was your impression?

Heyneker: [long pause] I had a lot of faith in Bob Swanson and the backers of Genentech that they would find the money to do the work. So I don't think that it bothered me that much if the contract was in place, yes or no. It is probably naivete or innocence, but at the same time I was convinced that what we were doing was very novel work, that we were on the right track, that we would be first to accomplish these feats—the cloning of insulin, the cloning of growth hormone. I mentioned naivete, or ignorance perhaps, because we did not know so much about gene expression. If you don't know what you don't know, it can't bother you. We felt, this is a promoter and we put a gene behind it, you solve most of the issues. It was so new and we were so ahead of the game, I felt that funding would be almost automatic.

Thoughts on Swanson's Motivations

Hughes: Because Bob was able to convince sophisticated people, like Tom Perkins, and established investment firms, such as Kleiner-Perkins, that Genentech was worth investing in, he must have had a charisma about him.

Heyneker: I'm not sure that it went exactly that way. Bob was looking for some work to do. He was working at Kleiner-Perkins, but he wanted to find himself an interesting idea to commercialize. I think he had read in the newspaper about some advances in recombinant DNA technology, and he felt, hey, it was time to commercialize. You know the story. He went to different players to talk about this possibility, among them, Paul Berg, Herb Boyer, and Cetus. It was Herb that told him that some of these practical ideas were doable. It was also a new field for Kleiner-Perkins. They were not investors in biotech. They give him a relatively small amount of money to try it out. I don't think that they were very sophisticated at analyzing this field and coming to the conclusion that Bob Swanson was the best. Bob Swanson happened to be one floor above Kleiner-Perkins. He happened to be formerly associated with them, and I think they felt compelled to help him a little bit. That's the way I think it went. But as soon as it became serious, I think they were very good partners for Genentech to have. I think it was a little bit serendipity.

Hughes: Yes, I hear you. How was Swanson as a sales person?

Heyneker: I think he was pretty good. At the same time, he was very young. He started when he was twenty-eight, if I recall correctly.

Hughes: Was he younger than you?

Heyneker: Oh yes, quite a bit. He had a young face. He was young.

Recombinant DNA as a Dislocating Technology

Heyneker: I think that he did a fantastic job, especially with Herb Boyer, to convince pharmaceutical companies as well as financial institutions that we were an exceptional company. But we were an exceptional company. We were the only game in town at that time. So recombinant DNA was really a dislocating technology in a dislocating situation. It's not the way biotech companies start now. If you have an interesting experiment in your notebook, that is not these days a reason to start a company. Genentech was started on much more of a broad-based, unique platform.

Hughes: Explain what you mean by dislocating.

Heyneker: Well, it was the first time in history that you could produce biologicals abundantly in a microbial species. It was made possible by recombinant DNA technology.

Hughes: Why do you apply the term dislocating?

Heyneker: Dislocating technology applies very well to recombinant DNA technology, especially when you look at the applications, at the possibilities, it opened up. That's what I define dislocating to mean. You needed this technology, and only with this technology was it possible to make these accomplishments, like producing human insulin in bacteria. That's dislocating. That's a completely different way of thinking. If you had asked any biologist in the pre-recombinant DNA era, they would not have comprehended it.

Hughes: "Dislocating" conceptually?

Heyneker: What I mean is a technology that did not gradually come about.

Hughes: I'm finally with you. So back to insulin.

Genentech's Aim to Limit Lilly's Expertise in Recombinant DNA

Hughes: Do you have any more observations about how the relationship with Lilly worked, and were there problems? After all, this was an unusual situation for a big pharmaceutical company to be in at this time.

Heyneker: Absolutely. I bet there were a lot of challenges. As you know, later on Lilly and Genentech didn't find themselves on the same side of issues. But I don't think that has much to do with the insulin project per se. It came about a little bit later when Lilly wanted to get into the recombinant DNA field in a more comprehensive way.

Hughes: Are you thinking of growth hormone?

Heyneker: Absolutely, and perhaps other proteinaceous materials. Lilly learned a lot from Genentech. They knew exactly how we made our constructs, how recombinant technology works. We taught them a lot. So, it was for them a relatively small step to apply this technology to other projects, and that was of course not the idea Genentech had in mind. We were not there to teach Lilly. We were collaborators with Lilly in the insulin project—end of story. At the same time, we can't stop anyone from doing recombinant DNA technology research, as long as they are not infringing our patents.

Hughes: Was the contract carefully worded, and did Tom Kiley draw it up?

Heyneker: I don't know.

Hughes: Was the contract intended to be limited to insulin rather than to transfer the technology generally?

Heyneker: I don't know. Well, the intent that I recall was to collaborate with Lilly on insulin and not to transfer the technology so that they could do whatever they want.

Heyneker Experiments

Hughes: Dave Goeddel told me that you liked to make small changes in research procedures to achieve greater efficiency.

Heyneker: Yes, he probably was talking about "Heyneker experiments."

Hughes: Yes, he called them that. [laughter] Give me an idea of what they might have entailed.

Heyneker: Well, they were sort of trial experiments leading to incremental improvements. I like to do that. I'm probably lazy, and therefore I want to be efficient.

Hughes: That's one way of looking at it.

Heyneker: We tried to make the technology a little bit better. For instance, we spent an enormous amount of time on proving that we made constructs in plasmids, so we had to do what we called plasmid preparations. That was monotonous, a lot of work, and it was often the numbers game to find the right clone. So the easier you could make the process and the faster you could make it, the less painful it was to do these procedures. I like to work on those sorts of projects, to make things easy, because it often goes hand in hand with robustness. If there are fewer steps involved, it makes it better.

Work on the Tryp Promoter System

Heyneker: I worked on looking for an improved promoter system. My lab was also involved with looking at secretion of proteins. It was not to find something totally novel, but how to make the procedure better. I enjoyed it very much. Those are experiments where you get your answer the same day, and you can very quickly see if you made progress. I still recall some experiments we did on the tryp promoter system, which were just wonderful. Very quickly did we learn that the system was absolutely more efficient for expression of recombinant DNA proteins. I got a lot of jollies out of that sort of work.

Hughes: How were you on long, drawn-out, sustained research?

Heyneker: We did one project later, urokinase, that was one of the long, drawn-out projects. Bill Holmes who was my dear technician and helper, the dogged guy, time and time again sorted through all these clones to find the thing that we were looking for. So, yes, in my lab we did that stuff, but it was not to the extent that Dave Goeddel did.

Hughes: I associate your name with the tryp system.

Heyneker: But, I'm not sure that the tryp project was a Heyneker experiment. It was more a project I took on to try to improve the levels of expression of proteins like insulin and growth hormone. What we have discussed so far was a promoter system based on the lac promoter. The reason was that the lac promoter system was very well understood from a molecular biology point of view and a genetics point of view.

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Heyneker: However, Charles Yanofsky at Stanford University focused on the tryp promoter system, while the lac promoter system was really Walter Gilbert's domain and also Art Riggs's. The tryp system had some unique properties. It was Giuseppe Miozzari whom we hired at Genentech, and who came out of Yanofsky's lab, who pointed us to the potential advantages of the tryp promoter. It was a good system to have controlled expression of genes. This system you can turn on and turn off quite nicely, very much like the lac system, which you can also turn on and turn off. But there were indications, and it turned out to be true, that the tryp promoter was a much stronger promoter. By stronger promoter, I mean it can more vigorously make messenger RNA, and therefore you can make more protein. And that of course was the name of the game; we wanted to make lots of recombinant protein. So, I did some initial work on the tryp system to dissect it and understand it better, and put bits and pieces of this tryp promoter system in *E. coli*, in the plasmid, and studied the effects.

Hughes: Now, was this system something that you could make on your own, or did it have to come from Yanofsky's lab?

Heyneker: Well, of course, you can always make those things on your own. But we did definitely get help from the work of Yanofsky, and Miozzari had access to this system, so we definitely had a head start. It was more important that we were not satisfied with one promoter system which worked reasonably well. In retrospect, it was a wise decision to

look at different promoter systems in comparative fashion, to understand expression better.

Hughes: Who took the initiative not to be satisfied with only the lac promoter?

Heyneker: [pause] I don't know who should take credit. I think Giuseppe Miozzari because he had worked with this promoter system for quite a while before he came to Genentech. He knew that system quite well, and he probably suggested, "Let's try it." It was I who took what he said and reduced it to practice. For instance, my lab made a fusion protein, not at the end of beta-galactosidase. It was very inefficient because you make a very long polypeptide of around a thousand amino acids, and then at the end of that, you make a very small polypeptide coding for insulin A-chain, insulin B-chain, somatostatin. So the ratio of what you want and what you make is not very efficient. You have to make a lot of protein to get a little bit out. So we wanted to shy away from that sort of system, and we wanted to have a system where the ratio was a little more balanced. We tested that out in the tryp system. I'm saying "we" because it is more than time that I introduce people who joined my lab over time. So it was really an effort of a group of people.

Projecting the Message of a Company Primed to Produce

Space and Equipment

Hughes: I remember vividly the story of Dave's and Dennis's first arrival at Oyster Point, and there was essentially one lab. By the time you arrived were there more labs?

Heyneker: No, Dave, Dennis, and I shared a room. I had a bench, and they had a bench, but we were building more small labs.

One of the first things we did was buy a big fermenter, a wonderful, colorful fermenter with red and green and all sorts of colors, which was placed behind a glass wall so visitors could look at it. It was basically a showpiece to let the world know that we were serious about producing products in *E. coli*, not just doing research in very small flasks. No, no, we were going to scale it up. I don't think that the fermenter had ever run, but it sent a strong message that we were on the way to becoming a pharmaceutical company.

Hughes: Was that Bob Swanson's idea?

Heyneker: Yes. I think it was a very good idea. So, we built offices and labs around that centerpiece.

Heyneker and an early Genentech fermenter *photo courtesy of Herbert L. Heyneker*

Strategic Hires

Hughes: Brian Sheehan was hired as vice president of manufacturing in December 1977. Manufacturing what?

Heyneker: Yes, that was sort of a problem. But again it sent a strong message to the community that we were serious about producing novel recombinant biologicals.

Hughes: Even though money was short? Was it wise to support a position which was premature?

Heyneker: [pause] Yes, in retrospect, it was not an essential hire at that time, and I think that it put Brian Sheehan in a pretty difficult position because he didn't have so much to do. He was very removed from all of the research, bench activities, we molecular biologists were doing. We were absolutely a different breed from what he was used to.

Hughes: So, what did that mean for interpersonal relations?

Heyneker: It made for a colorful mix of people, I would say.

Hughes: Is that an understatement?

Heyneker: Are you drawing me out?

Hughes: Only if you will allow it.

Heyneker: Yes, I think there were definitely some colorful people. We have not mentioned Sharon Carlock. She was Bob Swanson's secretary or assistant, also early on. We haven't mentioned the hire of Fred Middleton, which was also early on, and you can ask yourself the question, "Was it essential that we hired a chief financial officer at that time?" Although I think that Fred made some very good contributions, and probably it was not such a bad idea to hire him. He was also a good friend of Bob Swanson, and it must have helped Bob—it was his first real entrepreneurial job—to have some input from Middleton. But there were all these people who were hired at a time the company still had to grow to accommodate this. Sometimes you hire first, and then you build your organization around them. To surround yourself with high-quality people is still as of today a very sound way to go. Bob early on did a lot of things right, really a lot of things right. The business plan he wrote for Genentech was followed almost by the letter for the first few years. It's absolutely a remarkable feat.

Hughes: Do you believe that it was largely his work, as opposed to incorporating input from Herb Boyer, for example?

Heyneker: I think that a good business plan needs input from everybody. No one person can write a good business plan. That he got a lot of input from Boyer doesn't surprise me at all.

Sharon Carlock and Brian Sheehan

Hughes: Were there daily interactions with these colorful people?

Heyneker: That depends; some people tried to avoid daily contact with all of these colorful people. One of the great stories that Dave Goeddel told me was: Sharon Carlock was a forceful person, and Fred Middleton was not always prepared in the morning to face her. So he had the habit to sneak in the back door and in a roundabout way find his office so he would not have to talk to Sharon and answer to her first. That's in a figurative way. [laughter]

Brian Sheehan did not have full days of work most of the time, so he had to find some work for himself, so he became the manager of premises. Out of lack of things to do, you could find him with a broom, cleaning up his area, keeping it dust free. For us the molecular biologists who were working reasonably hard, it didn't fit exactly, and really it was a little bit sad. If I look back, it was probably not a good hire, and Brian Sheehan could not help us really. He was sort of premature. But still, from a psychological point of view, Bob accomplished what he wanted to accomplish, to show the world that we were not just a research boutique, that we absolutely were going to build a pharmaceutical company around this dislocating technology.

A Work Hard, Play Hard Culture

Hughes: The picture projected about the science in those days was of frenetic activity—working very long hours, broken up by pranks and practical jokes. Is that indeed a realistic picture of how it was?

Heyneker: We definitely subscribed to the saying that you work hard and you play hard. We definitely laid the foundation for Genentech's famous culture. Do you like that phraseology?

Hughes: Very good. You're getting the idea. [laughter] Do you want to expand on your comment about culture?

Heyneker: I recall that we were living in a building with hardly any windows—the labs were without windows, and only if you looked through the corridor, you got a glimpse of some office windows. Now and then we wanted to get out where the sun was shining. David Goeddel and I used to play racquetball in the back, between the two buildings. It was an area where trucks would come in to deliver goods. We would hit balls against the wall. Later, when the company grew a little bit, there was this club, Schober's, where people would go for a workout. Also there were racquetball courts. So then we became a little bit more professional. We played quite a bit of racquetball at Schober's.

Another example was that we had this hoop and a little Nerf ball, and we tried to put this little Nerf ball through the hoop. These were little gimmicks we used because your [experimental] reactions were incubating; you cannot always sit there and wait, or write

things up, and I was not very good at that anyway. So now and then we had to divert ourselves. The good news is that by doing so, you get to know each other quite well, and I think that that is an incredible advantage. We were really, certainly in the early days, a very collegial group of people. We all had a very similar goal, of being successful, of being first, and staying ahead of the game, and not because we had to do it; because we wanted to do it. We were incredibly proud of Genentech and what was going on. We were very excited about the technology we were developing. If people have a similar opportunity now, building something around a new technology, I think there would be an enormous amount of commonality. It was a terrific time.

Hughes: Well, you have founded several companies.

Heyneker: Later.

Hughes: Did you notice any similarities with Genentech in the start-up culture?

Heyneker: Well, the biggest difference was that later, you were not writing the book on recombinant DNA technology. It is more the norm that you have an idea and develop it more incrementally. It's more the way science is supposed to go.

Hughes: Normal science, to use Thomas Kuhn's term.

Heyneker: Yes, normal science, incremental, step by step. So, there was more competition. Those original days at Genentech were definitely unique, in more than one way.

More on Insulin

Competition

Hughes: Your passion for these new technologies has been a theme throughout these conversations. I'm imagining some of that passion is based on a vision of the possibilities, and the fact that there's a clean slate; there is nobody in front of you.

Heyneker: Exactly, although, of course, we were looking back and around us.

Hughes: Let's go back to that very issue of competition in the insulin story.

Heyneker: That's a good idea.

Hughes: You had competitors on several fronts. You particularly would have been able to grasp the capabilities of the UCSF team, having worked next to it.

Heyneker: Well, I saw with their cDNA technology at that time some real challenges. When you clone the gene, you don't have a lot of flexibility to get that gene exactly in the right reading frame behind the promoter sequence. We felt that was key, and I think that it is

key. Even after cloning the gene, it was not automatic that you could then express it. So, there were a number of challenges. At the same time, we knew that somatostatin worked. Therefore to make insulin A-chain and B-chain was not an enormous leap. I think the new challenge for us was later in the protein biochemistry—combining the chains. So, coming back to the competition, I felt that the synthetic DNA approach here was a leg up. And it turned out to be the case.

Hughes: So, the competition wasn't a tremendous worry?

Heyneker: Of course you worry. Also, the competition was dealt a difficult hand because of the [NIH] guidelines of cloning into different species. So, life was not so simple. As a matter of fact, I recall that Wally Gilbert and Axel Ullrich had to do some experiments in France to contain their work. But even then, I felt they would have benefited from combining their work with synthetic DNA capabilities.

Hughes: Where was the opportunity for them?

Heyneker: I'm not coming with solutions—certainly I wasn't then.

Hughes: I didn't phrase that right. Did they consider taking a synthetic approach? Did they have access to the technology?

Heyneker: I think they could have had access to the technology. Itakura was not the only game in town. Khorana was there. There were definitely other groups, also in Europe, as a matter of fact. Hubert Köster was very early on a player in the field of DNA.

Hughes: Where was he?

Heyneker: Germany. That would not have been a limitation.

Hughes: What does that tell you about the inventiveness of these different groups?

Heyneker: Well, let me turn it around. If I were in the shoes of Peter Seeburg or Axel Ullrich and I was very proficient in cDNA work—making cDNA from RNA—I might have said at least we should get the entire gene. Then we won't have to deal with the reconstitution of A-chain and B-chain, which is an unproven technology.

Hughes: All of these competing groups were working in academia where presumably they were less interested in the product, the application, than in the technology. They were experts in cDNA, so why would they take a synthetic route?

Heyneker: Exactly, I agree. That's what I was trying to say. If you are excellent in cDNA technology then why be distracted by chemical synthesis of DNA? Also, in academia, one of the real accomplishments is if you can publish your work and first demonstrate, let's say, the sequence of insulin, to understand how proinsulin works on a molecular level. So, there were a lot of motivations which had little to do with the production of human insulin. But I can't recall that we were really competing on expression of insulin. We felt—at least I felt—confident that we were ahead of the game. But Lilly hedged their bets, and not only did they support us, but they also supported the work at UCSF and I think also the work at

Harvard. I don't think that they were very open about it, and that doesn't leave a great taste.

Insulin Secretion in Culture ##

Hughes: I have heard that the way in which Genentech eventually secreted the insulin in culture was different from what other groups were attempting.

Heyneker: I don't think that we put a lot of emphasis on secreting insulin directly. I don't even know if we tried it. It was a very small peptide hormone, and we were afraid that it would be degraded. I wouldn't be surprised if we did experiments, and we were not very successful in direct expression. I'm on thin ice here, because it was a long time ago. Also, the process we transferred to Eli Lilly was basically the reconstitution of insulin based on A-chain and B-chain, and that worked. I think that we moved on to other projects.

Hughes: And left expression to Lilly?

Heyneker: Yes.

The Mini-C Project

Heyneker: We did the so-called mini-C project. Ron Wetzel was probably responsible for that project. So instead of producing A-chain separately from B-chain, we made a gene where A and B were on the same gene and connected by a gene coding for a connecting peptide, the C peptide, very much the way nature does it. The reason why we call it mini-C is that we came up with a shortened version of that C region. One of the reasons for shortening it was very practical: we needed to synthesize those genes by synthetic means, and DNA synthesis was still a lot of work, and we thought that we didn't need the entire C region

So, all of a sudden, we had now one gene which had insulin on its end. What I recall was that we still expressed that as a fusion protein. So now, by cleaving it with cyanogen bromide, you ended up with a peptide, which was A-chain, connecting peptide, B-chain. Then we hoped that the A-chain and the B-chain would find each other, which is quite logical because they were connected through the C peptide. They would fold as a proinsulin molecule, and then with proteolytic enzymes, you would cleave that C peptide away, very much along the same lines as nature. So that was our approach to make the process more efficient and also, hopefully, to make the refolding process more efficient. I think that that process was adapted by Lilly. Later, over time they switched to a process which resembles more the mini-C program.

Hughes: I remember Dennis saying that he, or perhaps someone else at Genentech, physically delivered two sorts of preparations to Lilly.

Heyneker: Could have been. But still with refractile particles, you would expect if you make something as a fusion protein, that's what you get. If you make something as a fusion protein, you can expect refractile particles. What happens is that the protein and its fusion partners are not a good match, and the protein cannot fold properly in a nice three-dimensional structure, and is no longer soluble. It is like the protein in a hard-boiled egg. You start with a raw egg, and its proteins are globular and transparent. As you cook it, you are interfering with all those nice globular structures, and you make some random polypeptide chains of amino acids. So, you lose its functionality and the proteins become aggregated.

Coming back to Dennis's observations and trying to give you my spin: I think we expressed mini-C as a fusion protein, and we could make a lot of that because it precipitated as refractile particles.

Hughes: Is it too early in the story to ask you for your observations about doing science in industry, as opposed to doing science in academia? Were you aware upon arrival at Genentech that the conduct of science was somewhat different?

Heyneker: I don't think that the conduct of science was different at that time. We were doing very basic research, geared toward practical applications. It was not a different type of work. But we did it not to understand a biological system in more detail; we did it to make a product. Our goal in the eyes of academic researchers was not as lofty. I never agreed with that and don't today. I think it was very lofty, and I and the rest of the Genentech team are very proud that we dedicated our research to these applications.

Specialization and Teamwork

Hughes: Did the early Genentech scientists immediately begin to specialize in certain aspects of a project, even though it was a team effort?

Heyneker: Well, Dave Goeddel and I were very busy with cloning, and that was our specialty. When Ron Wetzel and Mike Ross came on board, they were more in the area of understanding the protein part of it. So, from that point of view, you get already divisions. Roberto Crea, with his expertise in organic synthesis, needed a fume-extraction hood. For a lot of practical reasons, he found himself in a different laboratory from where we were. Over time, as an organization grows, yes, you get groups specializing in different aspects of the program. That happened at Genentech. And you can go on: You go from research project, to development projects, to manufacturing project. So, over time, as your organization grows, you will get—fragmentation is not the right word—but you will definitely get lots of different divisions, and it came pretty quickly. Genentech grew quite rapidly in the early years. They continued to grow very rapidly as a result of their success.

Hughes: Despite the specialization which you describe, I think of industry research as based more heavily on teamwork than in academia with its little fiefdoms. Despite the diversification at Genentech, there was still an overarching goal.

Heyneker: Absolutely, and I touched on that a few moments ago, and that still is true at Genentech. I think that's one of the advantages of working in industry. You should have overarching goals, and you should know what aspects you control in reaching the ultimate goal. In academe, the motivation is quite different. Graduate students are there to get a Ph.D. thesis, so they focus on their little aspect. That's all there is to it. They don't have to integrate it into a bigger project. The postdocs are there to make a name for themselves because they want to become assistant professors, so they have to publish. Those are often the most productive years. But again, the goal is very personal: "What contribution can I make to a certain understanding of whatever." It can be very individualistic.

In industry the goals are more clearly defined, but often you need different disciplines to reach them. So, indeed, out of Genentech came papers with twelve or fifteen names on them, and it was always viewed by academe as a funny way of doing science. I found to the contrary it was a very efficient way of doing science, because this was a demonstration that you can accomplish a lot by working together with different disciplines. We did definitely do science differently, especially when you look back in history. I think now the differences between academic science and more applied science are not that sharp anymore. [tape interruption]

Patent Issues

Hughes: There was a patent application on the insulin work, which became known as the Riggs-Itakura patent. My understanding is that the application was broadened to include the technology of the insulin experiment as well as that of the somatostatin—one application where I suppose it could have been two. Do you know anything about—

Heyneker: The politics behind this?

Hughes: It could be politics, but I was thinking of the rationale behind the choice to file for a broad patent rather than for two narrower patents.

Heyneker: No, that would be speculation on my part. When we did the work I knew too little about patent strategy and patentability in general to give you a meaningful answer.

Hughes: Presumably, you were working with Tom Kiley?

Heyneker: It's the obligation of the patent attorney to determine inventorship, and so Kiley talked to everybody who had an involvement in certain projects. He had to determine inventorship, and what inventorship means can vary over time. Is it just the person who comes up with the idea, or is it the person who comes up with the idea and reduces it to practice? That depends. Reducing it to practice can be very standard, and if you come up with some clever ways to reduce it to practice, it's quite different than just following protocol.

Hughes: The patent attorney communicates with the scientist not just to determine inventorship, but also to understand the science sufficiently to know where the claims are. Or is that one and the same thing? [tape interruption]

Heyneker: No, that's definitely not one and the same thing. I agree with you that the person that writes up the patent needs to know, pretty much in detail, how the experiments were carried out, and what can be claimed, and how you can extrapolate, if necessary. For instance, the somatostatin work teaches, to a certain extent, the insulin work; it lays the groundwork. But, at the same time, the insulin work has some other complexities. So it is not always a very logical progression. I would say the strategy with a patent application is to get broad claims, to fence off a big area, at the same time that a narrower area or a subset of the claims are truly protected. What you can cover in a certain patent needs to be determined by the patent lawyer, and also the strategy around it is very important—to eventually get a strong defendable patent.

Hughes: But, as you stated at the outset, these were not ideas that you had at the time. Academic scientists like yourself at that time didn't know much about intellectual property.

Heyneker: Correct. It's something that people are now much more aware of than in those days. My name is not on some of those patents, although I was involved in the work. I have no problem with it, because I think that inventorship is different than carrying the work out. If the straightforward way doesn't work, you have to invent around it to make it work. This is often an ongoing battle. It can well be that inventions are being made because one has to improvise.

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Hughes: Again, I ask about the setting. In industry the owner of a patent is the company, hence the inventors stand to gain nothing in terms of royalties. In academia, there's money involved. Money may have been at the root of some of the difficulties that occurred in the Department of Biochemistry at UCSF in the late 1970s when patents were filed on work that had been carried out by postdocs. And yet the lab directors were named as inventors. Why would a scientist in industry care if his name is on a patent or not?

Heyneker: Well, I should be agreeing with you completely, because there were definitely patents with my name on it where Genentech made enormous amounts of money and I didn't. But at the same time, I knew from day one when I signed up with Genentech that the patents were property of Genentech. I got stock in Genentech, and that stock became valuable, so that is one way to solve it. They could have had a slightly different policy that inventors on patents could share monetarily when money was being made on that patent. But in general that is not the rule among pharmaceutical companies. I think it is expected that you work there, and you get a good salary, and in the case of Genentech, you get a stake in the company that is compensation for all the work.

Hughes: People were satisfied with that system?

Heyneker: That question was never asked. That's the rule, and if you don't like it, don't work there.

Hughes: In theory—human beings are human beings

Heyneker: To gripe about it later is whining. Sure, I could whine, but that's the way it was. Policy varies very much from university to university. UC had a certain set of rules. You had to assign all of your patents to UC, but later when proceeds come out of these patents, they

get divvied up among the university, the inventor, and the department. Well, nice, but I don't think that it has anything to do with the fairness issue.

Hughes: I am interested in how much discussion there was between the scientists and Kiley or Bob Swanson or whomever it might have been about the importance of intellectual property—keeping good records, having notebooks signed—all that protocol. I'm picturing that Tom Kiley had an educational as well as a legal role to perform at Genentech.

Heyneker: I agree with you. We wrote things down in official Genentech notebooks. Some did it better than others, but that was indeed the assumption. All the notebooks are the property of Genentech. When a notebook is full, it will be filed, and I think that that is good practice. I'm convinced that this bookkeeping had been going on in the pharmaceutical industry forever. I don't think that this is something new or invented by Genentech. If after your academic career, you start working at Big Pharma, you go through the same culture shock. I don't think that was a novelty caused by recombinant DNA technology.

Hughes: You don't remember Tom Kiley coming around, leaning over your shoulder, and saying, "Are you keeping proper records?"

Heyneker: I can't recall exactly but that wouldn't surprise me at all, especially from Tom Kiley. He's quite a character, I would say. He would definitely explain to you in no uncertain terms the importance of keeping notes.

RAC's Ten-liter Fermentation Culture Limit

Hughes: RAC, the NIH Recombinant DNA Advisory Committee, as late as 1980 had a ten-liter limit on the culture medium used to grow up recombinant organisms.

Heyneker: Explain what happened.

Hughes: Genentech needed to make cultures in greater quantity than ten liters, and there was a problem getting permission to exceed that limit from the RAC, which was trying to work out its protocol for industry. In addition—and I know this was a concern of Swanson's—companies were concerned that proprietary information would get out during RAC's review. So, there was quite a bit of heat and fire around this issue at the time that Genentech was working with Lilly to scale up and get closer to an actual product.

Heyneker: Several notions here. First of all, Genentech had a special P3 room for work that needed guidelines, but I can't recall that we at Genentech had a great need for anything over ten liters. Lilly of course had a huge need for that. But Genentech itself, I'm not sure.

Hughes: Well, you mentioned the fermenter with all those bright colors. Apparently, right next to it, at least by 1980, was a much more capacious fermenter. To conform with the ten-liter limit, Genentech was forced to make repeated ten-liter batches.

Heyneker: That could very well be true.

Hughes: The irony was that right next to it was this beautiful fermenter with much greater capacity.

Heyneker: Was that to make insulin? Or growth hormone?

Hughes: I don't know.

Heyneker: We expressed growth hormone in 1979. For the record, Mike Ross and Ron Wetzel can give you much better answers here. But for insulin A-chain and B-chain isolation, I tell you, you can make a lot of A-chain and B-chain from a ten-liter fermenter.

Scaling up things to a really large scale brings with it a lot of technical problems. I cannot recall early on if we were working on these huge scales. Lilly did of course. They had to, especially since they brought this [human] insulin to the market so quickly. They must have put it in fermenters from day one, and I'm sure that they got dispensation from the RAC committee. So, if there was an issue with the RAC committee about scale-up, it was probably a short-lived issue. I can guarantee you that Lilly once and forever put this to rest, because it was a huge political issue that this [insulin product] should go through.

The Human Growth Hormone Project

Peter Seeburg's Postdoctoral Years at UCSF

[Interview 6: May 9, 2002]##

Hughes: Axel Ullrich and Peter Seeburg, the two UCSF postdocs, came to Genentech late in 1978, early 1979. How closely had you been following Seeburg's work on human growth hormone?

Heyneker: I was aware of his work, but not very intimately. We did discuss on a regular basis each other's work when we were having lunches together at UCSF, that sort of thing, but I can't recall that I had a very intimate knowledge of what was going on. I knew the subject, and I knew the programs to a certain extent

Hughes: Did he talk to you about some of the troubles he was having with Howard Goodman?

Heyneker: Problems in what regards?

Hughes: Well, there were several. He didn't feel adequately supported by his advisor, and there were tensions about not appearing on the patents that were filed by UCSF. I bring this up because I think they played a role in Peter's and Axel's eventual decision to come to Genentech.

Heyneker: Well, for the record, Peter Seeburg started work in Herb Boyer's lab. That didn't work out well, therefore, he went to Goodman's lab. There are, of course, different versions of

who creates a difficult situation. I definitely think that Goodman was still trying to establish himself as a top-rank scientist and therefore probably took more credit than he was supposed to take, especially in the eyes of the postdocs. But I don't know enough of the details about why I think it was a difficult time. In one area I was more intimately involved. When Howard Goodman was in Japan, and some breakthroughs were happening in his lab, he came back very rapidly, which was very understandable, and I think very positive. But perhaps he went a step too far by taking a lot of the credit. That was probably the cause of a lot of tension, and that probably helped to sway Peter Seeburg to come to Genentech.

Seeburg's Decision to Join Genentech

Heyneker: One of the first things I did when I came back to the States end of August of 1978 was to talk to Peter Seeburg and Axel Ullrich to try to convince them that Genentech was a very exciting opportunity. I do think that they believed that. In fact, Peter Seeburg studied the growth hormone genes because of his true interest in growth hormone and probably also in producing those hormones. Here's where academic interests merged with biotech interests. Those were very early days; we were creating a novel biotech industry. I think that Peter was definitely intrigued.

At the same time the work in his [UCSF] lab was going well, so it was not so easy to break things up, pack things up, and go to another place. But as of September 1978, when I talked to both Peter and Axel, I think that they were seriously interested. It was more of a timing issue of when they wanted to come. Then I think some of the difficulties Peter encountered in the lab helped him to move.

Hughes: Speeded up the process?

Heyneker: Probably, yes.

A Proof-of-Principle Project Turns Commercial

Hughes: Well, switching to the Genentech side of the equation, do you recall when the possibility of making growth hormone became one of Genentech's goals?

Heyneker: Well, very soon after I came there we started, probably because of Peter Seeburg's interest and the knowledge he had gained in the human growth hormone field. Growth hormone became a logical candidate.

Hughes: So growth hormone became a product actively to develop because you now had a new person, Seeburg, with capacity and experience in growth hormone? Rather than let's try to attract Seeburg to Genentech because growth hormone is on our product list?

Heyneker: I think that for the longest time the human growth hormone project was a proof-of-principle project more than a commercial project.

Hughes: Do you?

Heyneker: I know so. I think it was fortuitous and good follow-up that human growth hormone became truly a product. But in the beginning it was meant as a proof-of-principle product for the following reason: with insulin, we were expressing fusion proteins which we could clip with cyanogen bromide to obtain A-chain and B-chain, which then were reconstituted to form insulin. In the case of growth hormone, which is a much larger polypeptide or protein, those tricks we couldn't use. We could not make a fusion protein with the hopes of cleaving off growth hormone. There are a number of methionines in the human growth hormone gene which would make that strategy impossible. So, the challenge with growth hormone was to produce a truly new carrier protein in its entirety in *E. coli*. I would say definitely it was the next level of sophistication.

Deciding to Construct a Hybrid Gene

Hughes: Was there always the concept of combining the synthetic DNA and cDNA approaches?

Heyneker: I think that we came to that conclusion very early on, and the reason for that was pragmatic. With synthetic DNA, it is very doable to bring the structural gene in perfect proximity with the promoter sequence which expresses the gene. Especially in those days, to do it any other way could be quite cumbersome. So there were obvious advantages of using synthetic DNA to register the gene.

Hughes: Was there more than one other way?

Heyneker: Well, cDNA is the obvious way to go, but the initiation codon for any gene, the initiation ATG in the case of cDNA-derived growth hormone, is in front of a signal sequence and not in front of the mature sequence for human growth hormone. At that time, we knew very little; we were naïve about how we wanted to do it. The simplistic plan was to place an ATG in front of the mature gene of human growth hormone and ask *E. coli* to recognize that sequence, recognize that ATG, the initiation codon, and then right away make human growth hormone. By carrying out this process, we discovered later that there were a lot of things we didn't know. But since we are talking about the early phase, that was the plan. Now, to place an ATG in front of the mature human growth hormone gene by other ways was quite difficult, even today if you don't have access to synthetic DNA.

The UCSF Competition

Hughes: What turned out to be a race with the UCSF group on growth hormone—

Heyneker: Was it? [laughs in reaction to Hughes's use of "race."]

Hughes: Well, my understanding is that UCSF made an announcement on the same day that Genentech announced the successful expression of human growth hormone. UCSF had not actually expressed growth hormone?

Heyneker: No, they expressed part of growth hormone.

Hughes: Is that because they were using cDNA?

Heyneker: Yes, they made it as a fusion protein, which is fine. So they demonstrated that indeed the eukaryotic sequences coding for growth hormone were recognized by *E. coli*, a fact which in 1978 was unknown. There were a lot of signs which made you believe that prokaryotic and eukaryotic sequences could be quite different. One of the reasons was that it was hard to transfer genetic material form prokaryotes to eukaryotes. So, based on the knowledge at that time, it was not a predrawn conclusion that eukaryotic gene sequences would be recognized by *E. coli*, at least efficiently.

Hughes: So, that supposedly was their main purpose?

Heyneker: I assume. Look, if you didn't have synthetic DNA capabilities at that time, it was not easy to produce human growth hormone in its mature form in *E. coli*. I have mentioned it before in our discussions: what really helped Genentech enormously was our early recognition of the importance of synthetic DNA in cloning and expression. That is a statement that I firmly believe in. It was a fantastic tool.

Hughes: But couldn't you argue that that wasn't the point of what UCSF was trying to do? Or let's put it this way: what Genentech and UCSF were trying to do were two different things. The point of Genentech's work was to express a human protein.

Heyneker: Right.

Hughes: One could argue that that wasn't an interest of UCSF. I can see you disagree. They wanted to see if eukaryotic sequence could be expressed in *E. coli*.

Heyneker: Well fine, but I know Peter Seeburg and Howard Goodman well enough to know that this was only the first step. Of course the goal was to produce growth hormone in bacteria and not an inactive human protein. Perhaps another reason why Peter came to Genentech is because the focus of a biotech company is truly on making a commercial product. You can say that it was not the primary interest of UCSF, but I don't think that you have to be a rocket scientist to make that next leap.

Growth Hormone Expression Augurs Genentech's Success

Heyneker: Continuing on the human growth hormone story, the way that that the plan was carried out was quite straightforward and worked immediately. Once we had the construct made and put it in an expression vector system and produced in *E. coli*—I still remember

vividly when we did the radioimmune assay to check if we were producing something—the radioimmune assay was off the scale. It was so blatantly obvious that we were making a significant amount of growth hormone right off the bat. It was incredibly exciting.

Hughes: Who was there?

Heyneker: Well, it was Liz McCloud, later Liz Yelverton, who did the radioimmune assay. David Goeddel and I and Dennis Kleid were in a meeting with Bob Swanson. We showed him the results and it was absolute pandemonium. Don't forget that we were a fledgling biotech company, and to get a result like that, an early result, really meant, "Wait a second. We can do this; we can make foreign proteins in *E. coli*." That was really our goal. So all of a sudden we felt that the future of Genentech was guaranteed.

Hughes: In a way that it had not been with insulin?

Heyneker: Absolutely, because we were running out of other products to make with this fusion protein technology. Somatostatin and insulin were two candidates, and we were scratching our heads, "What's next?" So, we needed to go to large proteins.

Hughes: Now, Swanson, whom I interviewed many years later, also referred to the growth hormone success as a big boost to his goal of making Genentech a pharmaceutical company, in other words, doing all the steps in drug production itself. Do you remember him talking about that goal early on? Or did it become a possibility with the growth hormone success, and then he began to have that as one of the visions for the company?

Heyneker: Well, I can't recall when exactly this vision took place, but I know it was early. For instance, the fact that we had this fermenter put on the premises was basically to demonstrate to visitors and potential companies that we not only wanted to do research, but we also wanted to develop and manufacture and become a pharmaceutical company. Definitely, that was Bob Swanson's vision. With this early success in human growth hormone expression, our vision became much more of a reality.

Contributors to the Project

Hughes: Was human growth hormone one of your projects when you first arrived?

Heyneker: Absolutely, I was part of it, and David Goeddel. We divvied it up. I was going to do the assembly of the synthetic front part of the gene, and Dave was more the cDNA specialist. He would do the natural cDNA.

Hughes: The synthetic parts came from the City of Hope?

Heyneker: I'm pretty sure they still came from City of Hope. Roberto Crea, who was a postdoc in Keiichi Itakura's lab, came to Genentech during the early part of 1979.

Hughes: According to this chronology he arrived in September '78—the same time you did.

Heyneker: I doubt it.

Hughes: He's on the growth hormone paper.

Heyneker: Oh sure, he was definitely involved in the synthesis of the oligonucleotides leading to the synthetic front part. But what part he did at City of Hope, what part he did at Genentech, I don't know. He came to Genentech with the vision that synthetic DNA would continue to play a very important role, and that we needed that capability in house. Roberto Crea was a very logical choice. He wanted to join us, and he had the right experience.

Hughes: How were you doing with this division of labor?

Heyneker: Quite well, I would say. I think that we did not encounter many difficulties, because we put this whole research plan together quite well.

Seeburg's Contribution

Hughes: If that was the case, why did you need Seeburg?

Heyneker: I think that we had some difficulty, so perhaps I should rephrase what I said. It's so long ago to recall everything. The difficulty we had was with the cDNA part, and not because we couldn't do the cDNA work per se. But we had access to very poor material from which we could isolate RNA, like pituitary glands. They came from several sources, I think South America, and of course, they were isolated from human cadavers. We now know how quick and how careful you have to be to have fresh tissue fresh frozen and treated with certain agents to stop RNase in its tracks. But in those days that was not really well established.

Hughes: You hadn't encountered that problem with the insulin work?

Heyneker: No, because we synthesized the DNA.

Hughes: Oh, of course.

Heyneker: So, that was the problem. UCSF had access to better material.

Hughes: Through John Baxter, who was an M.D.

Heyneker: Exactly. So, it is a give and take. We had access to synthetic DNA; UCSF had access to the pituitary material. Perhaps the combination was ideal. Goeddel struggled because he tried to make high-quality cDNA with poor-quality messenger RNA. It's not easy.

Hughes: He knew that was the problem?

Heyneker: Yes, you can analyze the products, which you make on the gel, and you are looking for high molecular weight materials. If the whole thing becomes a smear on the gel, we know that the quality was not so good. It was frustrating. Perhaps in retrospect we

should have spent more time finding the right source for these pituitary materials. It was perhaps a little bit of ignorance or learning to feel our way around. We felt that Peter Seeburg, who had been there before, would be the ideal person to help us.

Hughes: Was it assumed that when Peter came, he would bring his UCSF clones?

Heyneker: I don't think that was the assumption. I think the assumption was that Peter Seeburg had the magic touch so he could repeat the work here.

Hughes: He wasn't hoping to utilize his relationship with Baxter to get a better source of RNA?

Heyneker: I don't know if he got better pituitary material. If I were Peter, that would definitely be one of the first things I would do—get good pituitary material. He is a very smart guy, so it wouldn't surprise me if that's what he did.

Hughes: So, may I conclude that by the time Seeburg arrived, the growth hormone project was going pretty well, except for the cDNA component?

Heyneker: Right.

A Shift Towards Research as a Team

Hughes: So what Peter Seeburg was expected to do as soon as he settled in at Genentech was to get that roadblock cleared away?

Heyneker: Well, indirectly. When Peter Seeburg came to Genentech, it was more than logical, with his pedigree and background in this area, that he would lead the human growth hormone project.

Hughes: How did you feel about that?

Heyneker: I was not leading the project. I never felt bad about it. On the contrary, the goal was really, how quickly could we do this? I think we were quite corporate at that time in our thinking. We felt very strongly that we wanted to build a successful company. That was the most important aspect.

Hughes: I'm assuming that you would have had quite a different feeling if you had still been lodged in a UCSF laboratory.

Heyneker: Probably, but we were getting into a type of research where in order to make quick progress, you need the help of other experts. So, to do a whole project alone so that you can claim ownership was changing to a certain extent, and it kept changing at Genentech because the project—

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Hughes: It seems to me that's a big change from academia where there are islands of research in a department, and a lot of emphasis on priority and ownership.

Heyneker: I probably look at it differently now. I know there were instances where I felt strongly that I deserved first author ownership, and other times I was very grateful that I could be put on a paper. So, it spanned the whole range. Perhaps there was a change going on that more people got involved in a project. In Herb Boyer's lab, we were doing quite a few projects in collaboration. I recall that I worked closely with Paco Bolivar, and that we both made contributions. We were so excited about the progress that we made that I can't recall that I ever felt bad.

Seeburg's Slow Start

Hughes: So what happened after Seeburg arrived?

Heyneker: [pause] Well, it was a difficult transition period for him. I don't think that he was immediately very gung ho. It was a slow start for Peter, and we needed to push him quite a bit. Mainly David Goeddel needed to push him quite a bit. So, I think it turned out that Dave probably did a lot of the work.

Hughes: Dave told me that in about February 1979, he more or less took over the growth hormone project. He had been working on interferon. We shouldn't forget that there were several research projects going on simultaneously at Genentech.

Heyneker: You're right. I think that Peter needed time to make that transition, and it was a slow process. We were in an incredible hurry, so we didn't find time to wait.

Constructing the Synthetic Portion of the Gene

Hughes: Were you still associated with the growth hormone project?

Heyneker: Yes, because I think I did the front part. I cannot recall what the order was, what was done first. I think I was waiting for the oligonucleotides to arrive, so my task became easier and easier because the enzymology of stitching the oligos together became more and more worked out. I don't remember that I had a hard time.

Hughes: Worked out at Genentech or worked out at a variety of institutions?

Heyneker: Both. But at Genentech it became easier and easier; we optimized the system. Also, the quality of the oligos probably became better and better. Keiichi was not sitting idle at the City of Hope. He constantly improved on the chemistry.

Hughes: By this time, which was now early 1979, could you buy a lot of the enzymes?

Heyneker: I think you could. It was the beginning of being able to purchase them. Remember, before I went home at the end of '77, I spent a week at Bethesda Research Labs. So, yes, I think you could buy restriction enzymes at that time, and probably ligase and polymerase, although we still were making our own enzymes at Genentech. It was cheaper; we could make abundant amounts of enzymes, and not all enzymes were for sale. I do remember that I continued to make batches of enzymes, and I taught a lot of people to do that.

Hughes: When somebody needed an unusual enzyme, was it automatic that they thought of you? Were you still Mr. Enzyme?

Choh Hao Li and the Amino Acid Sequence for Growth Hormone

Heyneker: Perhaps I didn't give them a chance to think of me; I probably was already participating.

Hughes: I've heard that the human growth hormone gene is about four times as large as the insulin. Did that present intrinsic difficulties?

Heyneker: At that time, to synthesize the entire gene, we felt was an overwhelming task. Moreover, we did not know exactly what the amino acid sequence was in human growth hormone.

Hughes: Oh, really?

Heyneker: It was published by a guy from UCSF, as a matter of fact. What's his name? You can figure it out.

Hughes: Choh Hao Li.

Heyneker: Yes. He determined the amino acid sequence. But once we had isolated the cDNA, and sequenced the DNA, and deduced the protein sequence from the DNA, it turned out that there were two positions in which Li had made a mistake. I'm not saying that in a negative sense. In those days to sequence a protein of that magnitude—around molecular weight 24,000, 21,000, somewhere in that range—was an enormous task. It is easy to confuse certain amino acids. I think it was a darn good sequence. But once you have DNA sequence analysis, it's so much faster and more accurate that we could establish a more definitive sequence.

Hughes: How was Li doing it?

Heyneker: Well, I think that he used the Edmund degradation protocol, which was probably established in the sixties. Time consuming, difficult. It must have been frustrating to spend years and years of your life to do that, and here comes a novel technology, namely cloning, and you really know the answer with higher accuracy, in a matter of weeks, in those days. Now, cloning and sequencing is a matter of hours.

Christopher B. Anfinsen spent a good part of his life sequencing albumen. We cloned the albumen gene at Genentech and determined that there were five or six mistakes, and we did it in three or four months. I remember that I felt almost sorry for Anfinsen, who spent so much time doing this—it was absolutely state of the art—but a new technology can completely supersede it.

Adopting the Tryp Promoter for Protein Production in *E. coli*

Hughes: We talked in reference to insulin about Miozzari's introduction of the tryp promoter from Yanofsky's lab. I believe it was also used in the growth hormone work. When did that come in?

Heyneker: The original plan was that we would use the lac promoter to express human growth hormone. We got the first excitement from work done in that system, which we published soon thereafter in an article in *Nature*. Of course, we wanted to make a lot of product in *E. coli*, and we felt that the lac promoter was a weak promoter and that there were much stronger promoters. Stronger means that per time unit, you would make more messenger RNA. That's probably the best way to explain it.

Giuseppe Miozzari had quite a bit of experience with this tryp promoter system, and he made the suggestion that I should look into that. That's exactly the type of experiment that I like to do. So I took part of it and built a plasmid with this tryp promoter system. It was not only used for a growth hormone, but it became sort of the workhorse to express foreign proteins in *E. coli*, including insulin. We made a fusion protein, which was no longer the beta-gal fusion protein, but was a fusion protein between the tryp LE and our insulin. [tape interruption]

So, coming back to your question, we developed a tryp promoter system because we felt it was a much stronger promoter. It was also a promoter which could be controlled with indol acetic acid. So we could turn the promoter on and off at will with a chemical which was cost effective and not as expensive as some chemicals used to turn on or off the lac promoter. The tryp promoter system, either in conjuction to express fusion proteins or to express proteins directly, became the workhorse to produce proteins in *E. coli*.

Hughes: Was there any adaption of the tryp system that had to be made for expressing different proteins?

Heyneker: Well, we adapted the system in such a way that we placed an EcoR1 site in the same position where we had an EcoR1 site in the lac promoter system. Therefore we could exchange genes quite easily. It became a very portable system. So, yes, it needed some adaptation to do that, but also to make sure that the promoter sequence was aligned properly with the structural gene. Those were things that needed to be done, but we did not encounter problems with it. What we did encounter was that it worked like dynamite. It was a very good system.

Using Bacteria as Protein Factories

Heyneker: I recall that I went on vacation or a trip, and Dennis Kleid helped with that system. He was first to test the new tryp system, and he was absolutely amazed how much more protein we were making. He also demonstrated that the fusion protein was precipitated. When you looked under the microscope at these bacteria, you saw these gigantic inclusion bodies. It looked as if the bacteria were chock full of the desired protein. Fortunately that protein was in a form that will precipitate, which is not the natural form because it should be soluble. I think it was Dennis Kleid who came up with a way to purify those inclusion bodies. It became a handy way to get rid of a lot proteins and concentrate on the inclusion bodies, and then, in a refolding protocol, re-solublize the human growth hormone. That became the standard for quite a few different proteins.

Hughes: Was that proprietary information?

Heyneker: I wouldn't be surprised if we kept that proprietary.

Hughes: Dennis made the point that other people, such as Gilbert, were trying to secrete insulin into the medium in a way that made it more difficult to purify.

Heyneker: I think Dennis is right. It was a very good observation, and we made the best of it to capitalize on it.

Hughes: If the insulin particles were visible under a light microscope, why weren't other people seeing them?

Heyneker: Very good question, Sally. The reason was that we were the first to do this!

Hughes: [laughs] Touché.

Heyneker With the lac system, because the expression values are so much lower, we didn't see them. Once we analyzed the amount of material we were making, it was surprising how much material we were making. We were truly using bacteria as little factories. So because of that, we investigated in more detail and found out that the bacteria looked quite different.

Devising a System to Purify and Re-fold Human Growth Hormone

Hughes: I read that you were working on a signal sequence using a different bacterial species.

Heyneker: Yes, I'll come to that. Okay, so here we had a system to produce lots of human growth hormone, and it could also be folded, and it could be purified to homogeneity, except that the *E. coli* did not remove effectively the first amino acid, the methionine. So, the product we were making was met-hGH, which was a pity. The biological activity of met-hGH is exactly the same as that of hGH. But it was not ideal because the competition could always say, "Your hGH is different from the real hGH." So we wanted to develop a

system where we would end up with the real hGH. The way nature makes real hGH is to make a precursor form of hGH which includes a signal sequence, and this prepro-growth hormone would then be proteolytically matured into hGH.

We decided to try to mimic that system in *E. coli*. We decided to make a fusion protein where we used a signal sequence from bacteria to which we fused the mature gene of human growth hormone in the hope that *E. coli* would recognize that signal sequence and would cleave it off at the right position. Bingo, we would end up with true met-less human growth hormone, secreted most likely in the periplasmic space. Don't confuse that with secretion into the media. *E. coli* is not a microorganism which has the capability to truly secrete into the media. It secretes from the cytoplasm into a space between the cytoplasm and the outside of the bacteria. It's called the periplasmic space.

Hughes: Why would nature want to do that?

Heyneker: Well, the short answer is that *E. coli* was never meant to produce human growth hormone.

Hughes: So *E. coli* tries to get rid of this garbage by precipitating it?

Heyneker: No. We were trying to piggyback on the system that *E. coli* had developed for its own good, namely to secrete proteins into the periplasmic space. Some of these proteins are probably used by *E. coli* for defense mechanisms. So, if you get an invasion from the outside, I can imagine that some of these products secreted into the periplasmic space might be the first line of defense. But I promise you that at that time I did not ask that sort of question. I wanted to use the bacterial system to secrete human growth hormone into the periplasmic space. That was work Greg Gray was involved in. He came as a postdoc to my lab. He took it upon himself to work it out—and successfully. We started with the signal sequence, which came from a bacterial toxin, colicin, colicinogenic factor, which *E. coli* uses to secrete into the periplasmic space. I thought that toxin might have a very efficient signal sequence, which *E. coli* recognizes with great efficiency.

Hughes: You were delving around in the literature?

Heyneker: I discussed it with a colleague, Professor Werner Maas at NYU. He had a lot of experience with this system, and we collaborated on this system. I think we helped to determine the sequence of this signal sequence, or we sequenced the entire toxin, in collaboration with him. Then we used that sequence to put in our system. I'm not sure exactly how that came about. [tape interruption while Heyneker reflects]

As I mentioned, in collaboration with the lab of Werner Maas, we worked on this signal sequence. As a matter of fact, we published a paper on the nucleotide sequence of the gene for heat-stable enterotoxin II of *E. coli*, which was published in *Infection and Immunity*.[4] What Greg Gray did was to assemble in a plasmid a tryp promoter system, this enterotoxin signal sequence, followed by the human growth hormone gene. Lo and behold, we made large amounts of secreted and correctly processed growth hormone in *E. coli*. No inclusion bodies—perfect growth hormone of exactly the same sequence as you find in nature.

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4. See Heyneker bibliography #36.

Hughes: In the cytoplasm?

Heyneker: In the periplasmic space. You can purify those periplasmic proteins quite nicely because you can enzymatically digest the cell wall of *E. coli*, and by doing so you will release all the periplasmic proteins. But the rest of *E. coli*—which is the majority—remains intact and you get rid of it.

Growth Hormone as a Model System

Heyneker: Now, I should stress here that all this work with human growth hormone we did over the years. The work on secretion, both in *E. coli* and also in another microbial species, *Pseudomonas*, was finished around 1983. What I would like to say here is that human growth hormone was a fantastic model system. We could not go wrong with human growth hormone. We could express it in good amounts with different expression systems. We could express it as an inclusion body and then refold it, and we could also secrete it with high efficiency. It was a wonderful model system to learn from and to make product.

If we had started with another gene—let's say the gene for alpha interferon—without the knowledge that we could make eukaryotic proteins in *E. coli* with high efficiency, that it might have set back the whole field, because we might have been frustrated with the lack of progress and blamed it on the fact that there were other differences between prokaryotic and eukaryotic genes we did not understand.

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Heyneker: At first we could not see or detect any amount of alpha interferon, which was very disturbing, because we had a collaboration with Hoffmann-La Roche on this project.

So what I'm trying to say is that we had this example that we could produce eukaryotic proteins in *E. coli.* There was not a barrier, as people had feared, between prokaryotes and eukaryotes. We didn't believe it existed. But if we had started with alpha interferon, we might well have thought that it existed. It was extremely disappointing how little material we made. We could not even detect it, and we had very sensitive assays for detection. It took quite a bit of work to solve that problem. Changing from the lac system to the tryp system helped some. But again, having the knowledge that you can make these proteins means that it is a solvable puzzle.

Hughes: Are you saying that otherwise Genentech might have given up on alpha interferon?

Heyneker: Exactly, it might have been quite disappointing, because even if you made a little with a lot of effort, the purification would be a daunting task. Don't forget, you don't want to inject lots of *E. coli* proteins into patients, so you need a high level of purification.

Hughes: There's the commercial imperative popping up again.

Recognizing Growth Hormone as a Viable Commercial Product

Heyneker: Absolutely. I think the growth hormone story was a glorifying success. We were very lucky that we chose that system. On top of that, it turned out that growth hormone was indeed a very viable commercial product, and that it was a very smart thing to develop commercially, especially since with its orphan drug status, it prevented other companies from entering the competition early on. It was a success all around.

Hughes: Are you saying that its commercial success was an unexpected bonus?

Heyneker: Absolutely. I think Bob Swanson had an open mind, but he did not see this originally as a real product of any value. He thought that the world market was around twenty million or thirty million, at best.

Hughes: There was some further serendipity. You had at first the natural pituitary hormone to compete with. But in the mid-eighties—

Heyneker: Creutzfeldt-Jakob disease was associated with it.

Hughes: Which turned the tables, because the FDA had been making quite a bit of trouble about whether the methionine form of growth hormone should be approved or not. It's probably simplistic to say that the Creutzfeldt-Jakob problem didn't hurt the fortune of Genentech's growth hormone.

Heyneker: On the contrary, I think it really helped. I am convinced that it definitely helped the patient population as well. It not only helped Genentech; it also helped the patient. I think that the FDA realized this, and that it was the smart thing to do. Dwarfism is a major, debilitating disease, and to have proper treatment is very important. I'm very proud and excited that I could participate in the development of the drug, and I think that it is quite important.

More on the Genentech-UCSF Competition

Hughes: Let's return to the subject of Genentech's UCSF competitors. Genentech announced the cloning and expression of the growth hormone gene after Goeddel had given a paper at a Miles symposium. The very next day, Genentech made an announcement, and UCSF also raced to get an announcement out. Then UCSF beat you to the punch, so to speak, by publishing first.

Heyneker: No, I don't see it that way at all.

Hughes: How do you see it?

Heyneker: Well, we've come full circle. I said that in the beginning our announcement was that you could make human growth hormone in *E. coli* in a biologically active form. What UCSF

had done was to make a fusion protein which is not the biologically active form. I think that it was a significant difference.

Hughes: Do you think that the scientific community recognized the difference?

Heyneker: I don't know. I hope so. I think so. The reason I say so is that Genentech had made production of bacterially expressed growth hormone a reality.

Wider Applications of Growth Hormone

Hughes: Your paper mentions other possible applications of human growth hormone, for example, in wound healing and burns. How does a company decide when it is appropriate to extend the use of a drug created for one purpose to applications in other areas? Which is true of—

Heyneker: Many drugs. Although I don't think that growth hormone is being used in wound healing. It is being used by athletes who want to perform more, and also by children who are not truly dwarfs but fall under the fifth percentile or tenth percentile of the growth curve, and that's quite helpful. After all, the decision what is a dwarf is arbitrary, so since there is now enough growth hormone available, you can address other markets. Once a drug is on the market, M.D.s have quite a bit of flexibility to test it for other purposes, especially when safety has been established. You see it over and over again. Today, the most amazing new use for a drug is the announcement that the statin drugs seem to have a dramatic effect on prevention of Alzheimer's disease. Nobody would have thought about that when the drug came to market, but you find all the sudden associations and other indications. So it happens over and over again that the scope of a drug becomes wider.

The Role of KabiGen

Hughes: Am I right in thinking that Kabi supported the early basic research on human growth hormone, not just the scale-up?

Heyneker: I think that there was a lot of interest on the Kabi side to be involved in all aspects of the project. As a matter of fact, they paid for it. So they had the right to know what was going on. But I think that scientists at Kabi were truly interested to see our progress. I remember that on several occasions I went to Sweden to give an update. The coordinator there was Bertil Aaberg. He was a terrific guy. I think we had very good interactions early on. I'm not sure how business discussions went, because that was more Bob Swanson.

Lilly and the Competition Between Met and Met-less Growth Hormone

Hughes: How did Genentech's interaction with Kabi compare with that with Lilly?

Heyneker: It was a little bit more competitive with Lilly. Once we demonstrated that we could make insulin on a very small scale, they took over and scaled up. It was less of a collaboration. It was more: "You'd better reach your milestone or else." The relationship with Eli Lilly deteriorated rapidly because they started to dabble in the human growth hormone field and tried to declare all our patents and intellectual property invalid.

Hughes: Yes, and Lilly also came out with a met-less form that was approved by the FDA even though your met form had been previously approved.

Heyneker: Right. I think we made some mistakes. We had our met-less hGH, the secretion system, but we had spent so much effort, time, and money with the met-hGH that we did not convert to the met-less hGH early on. Perhaps we couldn't afford it. There might be financial reasons why we didn't do it. But I felt we should have switched as soon as possible to the real thing, thereby preempting other people from entering the market.

Hughes: But you had made the point earlier that in terms of the biological effect, the two products did the same thing.

Heyneker: Well, we always worried that met-hGH would be more antigenic than met-less hGH.

Hughes: Was there any evidence that it was?

Heyneker: It is extremely hard to say because with either product there is antigenicity, and the reason is that you often give a big bolus of human growth hormone, which then should last for a week or two, whatever. By doing so, you always run the risk that you activate the immune system. You might overcome tolerance and induce some antigenicity, which did not really threaten. But it is extremely hard to differentiate antigenicity caused by that extra met, or antigenicity in general, because both products give it. I think it was not a real problem. If we had seen serious antigenicity and could prove that it was directed at the end, we would have been in trouble. But I know it didn't happen

Hughes: I believe that the growth hormone contract with Kabi, as well as the insulin contract with Lilly, were written with the objective of providing the technology solely for those products.

Heyneker: Absolutely.

Hughes: How indeed could that be done when there was human interaction occurring on many different levels between Genentech and the two companies?

Heyneker: Well, I think that you are touching here on something which is hard to put into words in a contract. It also involves human decency. Lilly knew very well that we developed all the cloning technology. Whatever they learned from us, came from us. Then to develop it in parallel and say, "All the technology that you developed is useless, because we are going

to attack all of your patents." I think that it's hitting below the belt, and I think it was not very ethical. But you often see that. There's a lot of money at stake.

When Genentech fell on hard times and Roche bought into Genentech, the lawsuit with Lilly was resolved literally in a matter of months, because all a sudden Lilly realized that Genentech had very deep pockets. I am very disappointed that money talks here. A small company can be right, but that doesn't mean that you will win a lawsuit, and especially here in the United States that is often the case.

Genentech's Settlement with UCSF at the Time of Its Initial Public Offering

Hughes: There was another time that money talked. Well, I'm sure there were many times that money talked. In 1980, just before Genentech's IPO, there was a controversy with UCSF over whether materials had been unjustifiably transferred to Genentech. Swanson and Kiley, in order to be done with this matter because the IPO was pending, paid UCSF a considerable sum of money.

Heyneker: Correct, but that didn't stop UCSF from continuing the lawsuit.

Hughes: Right then and there?

Heyneker: No, later.

Hughes: Did you know about the settlement?

Heyneker: I knew that Swanson and Kiley wanted to settle the whole thing and did pay UC a serious sum of money.

Genentech's Settlement in the Case of Urokinase

Heyneker: There was another occasion involving urokinase where we ran into Abbott. Abbott claimed that they had also cloned urokinase. It was a total fraud, and everybody knew it was fraudulent, but it didn't stop them from harassing Genentech. Genentech in the end allowed Abbott to commercialize urokinase. We will come to this. [tape interruption]

Comments on the FDA Approval Process for Human Insulin and Growth Hormone

Hughes: It took a while for the FDA to approve growth hormone. The expectation was 1984, but it took almost a year longer. You have a comment to make about the approval process.

Heyneker: Eli Lilly got incredibly fast approval for insulin, while it took Genentech much longer to get approval for human growth hormone. There are good reasons for that. Eli Lilly has a long track record of making safe drugs. They are a known manufacturing entity, while Genentech had to learn all of these things. So I can imagine that the FDA scrutinized Genentech a little more. Also, from a public health point of view, insulin is very important. The amount of insulin the United States needed over time was increasing every year with a graying population. You could do the calculation that at one point in time there might not be enough insulin around from porcine or bovine sources. Therefore, it could become an emergency. Recombinant human insulin was a way to solve this problem once and forever. So I think this had much to do with insulin's early approval. In the case of hGH, there was a need for a high quality, safe product, but there was not the same urgency to get hGH approved before appropriate testing.

Bovine Growth Hormone

Hughes: Tell me about bovine growth hormone, which was eventually licensed to Monsanto.

Heyneker: We felt that once we had cloned human growth hormone, the cloning and expression of bovine growth hormone, porcine growth hormone, and all other sorts of growth hormones would be a piece of cake— just follow the same track. The cloning from cDNA by that time was very straightforward. The pituitaries from cows and pigs, we could isolate at will—and obtain high quality material. That was all simple, and sequencing became easier and easier, so those were projects which didn't take that long.

However, when we cloned the bovine cDNA and then expressed it in analogy with the human system, we hardly saw any bovine growth hormone being made—significantly less, a hundredfold less at least, and very puzzling. We didn't understand it because the hook-up was perfect. It was sequenced and resequenced. So it turned out almost by coincidence that we shortened the plasmid at the end. The 3-prime untranslated region in bovine growth hormone was a little bit longer than it was with human growth hormone. But it was outside of the coding region, so it was after the stop codon, and we did not anticipate that it had anything to do with expression. But when we took it out the whole problem was solved. All of a sudden we were making grams and grams of growth hormone per liter—at least as much as we made with human growth hormone. We discovered that this 3-prime untranslated region, even in *E. coli* expression, could have a major influence on expression levels. We solved the problem, but we never realized until then where the problem lay.

Hughes: Did that information help you in other projects?

Heyneker: Absolutely.

Hughes: Did you publish it?

Heyneker: I'm not sure about that. Perhaps at one point in time.

Genentech's Publication Policy

Hughes: How was the decision made about what to publish or not? Who was in on that?

Heyneker: I think Kiley was in on that. The scientists were very much involved. There are two ways to protect your intellectual property rights. You can either follow the route of patenting or you can follow the route of keeping things proprietary. The risk of keeping things proprietary is that you might lose a patent situation or patentablilty. If it leaks out or a lot of people independently come to the same conclusion, and if they patent it, you're out of luck. So it's a balancing act. Some of the things which are very hard to police, you might as well keep proprietary. There was clearly the spirit that we wanted to make Genentech a very successful company, so it was not really an issue what we should publish or not publish, or patent or not patent, or what the order was.

Hughes: But high numbers of publications helped Genentech as well as the authors. I've heard university scientists use Genentech's publication record as a standard for their own institution to beat. They were being outshone by a commercial entity.

Heyneker: Well, I think that it is a very interesting subject you are touching on. We made a conscious decision to publish as soon as we had seen the patent office. Also we made a conscientious decision to publish with a lot of names on the paper to show the world what you can do if you put your mind to it and your research to it. The result was that Genentech was viewed as a biotech company which was commercializing biological research, and a lot of scientists in those days were a little wary of that. At the same time they admired us because we had a free publication policy, and the quality of the papers was of course quite good. It helped us to attract the best scientists. So, I totally agree with you that our policy was the right policy.

Hughes: Were you in on the formation of that policy?

Heyneker: I can't recall.

Hughes: The story goes that Swanson took some persuading to be convinced that publication was a good idea.

Heyneker: Yes, I subscribe to that. It was Herb Boyer who really had that vision. The credit should go to Herb Boyer.

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Hughes: After bovine growth hormone, there was a narrowing of Genentech's research focus.

Heyneker: Oh yes, we had to. We had our plate full. We were definitely focusing on human pharmaceuticals.

Hughes: But not in the beginning. There are business plans as early as the 1970s which mention creating products for animal husbandry and the enzymatic work that became Genencor. It was a very diffuse program.

Heyneker: Well, I think Genencor is a good example that Genentech capitalized on all its technology, without exposing and confusing or diluting its resources inside Genentech. I think Genencor was a successful spinoff.

Hughes: Was the spinoff idea well established inside business circles, or is it something that biotech and the Silicon Valley phenomenon invented?

Heyneker: Genencor started in 1983, so there were quite a few biotech companies at that time. That spinoff idea was probably borrowed from Silicon Valley. Genentech tried also to do something with an instrumentation company. It was a joint venture between Genentech and Hewlett Packard, called HP Genenchem, which was not a success. It dissolved a year or so later. Also Genentech had a vaccine effort which they wanted to spin out. Well, perhaps we should talk about it next time. Jack Obijeski was hired to lead that.

Thymosin-alpha 1

[Interview 7: May 14, 2002]##

Hughes: Let's start with the thymosin-alpha 1 project.

Heyneker: Yes, thymosin-alpha 1 was a project which was brought to Genentech's attention by one of its advisors. His name was Allen Goldstein. He was studying that molecule and its biological properties in his lab, and I forget where it was exactly. This type of peptide hormone molecule fitted very well in with the way we did somatostatin and the way we expressed insulin, namely as a fusion protein. Again, with alpha 1, there is no internal methionine, and therefore we could cleave off the biologically active peptide by cyanogen bromide treatment.

It was a project we did on the side. We had gained quite a bit of experience with synthetic DNA. Roberto Crea was on board. We had this synthesis capability in house. The quality of the DNA was getting better and better. Projects like alpha 1 became very doable, and it turned out that way. It was a matter of putting a gene together, expressing it as a fusion protein, and then Ron Wetzel from the protein chemistry department took over. He did the cleavage and purification and further analysis. The product never went any further than that. We didn't commercialize it. I don't think there was truly real value to be had there. We did it, and we probably shelved it.

Hughes: Did you have potential applications in mind?

Heyneker: Not me, but Allen Goldstein did. I think that he used the molecule to compare it with naturally occurring alpha thymosin. It worked but the application and the opportunity were not there.

Hughes: Were you working on it directly?

Heyneker: I was directly involved in yet again putting the gene together. That was my specialty.

Hughes: How do you and others on the team feel when something gets shelved?

Heyneker: I cannot recall whether it was a huge setback. It was a speculative project anyway. We felt that at that time we had bigger fish to fry, like interferon, urokinase, tPA. Those things were coming along as opportunities. Also, the fact that we could express bigger proteins, like human growth hormone. We were no longer dependent on the limited number of peptides, like insulin, which we could express as a fusion protein.

The Interferon Projects

The Scientific Challenges

Hughes: Interferon is a very large subject in the early history of Genentech. Because you were not directly involved, maybe we can leave the ins and outs of this story to those that were. [5]

Heyneker: That's a good idea. As a matter of fact, I recall that we did discuss certain aspects of alpha interferon already. It came up when we were discussing expression of human growth hormone. I said if we had started with alpha interferon, it might have been a completely different picture, because we had a lot of trouble expressing alpha interferon when we hooked it up for expression the same way we hooked up human growth hormone. It was very puzzling. It took a long time before we got it to work. The cloning of interferon was already a challenge in itself—quite a rare low-abundance messenger RNA signal. Therefore it was more difficult to isolate it from the mixture of messenger RNAs. Also, not much was known about it—and this is an interesting story.

Obtaining the Amino Acid Sequence

Heyneker: I recall that it was very important for us to get some amino acid sequence of the hormone in order to make probes. With these hybridization probes we could screen libraries of clones which contained plasmids, and these plasmids had all sorts of different cDNA inserts. We screened these colonies with a probe which we felt was specific for interferon. So, we did not have access to interferon directly. We did not have access to the amino acid sequence. We knew that some of the amino acid sequence of interferon was going to be announced at a meeting. We were sitting there, and as soon as the amino acid sequence was flashed up on the screen at this scientific meeting, we furiously wrote down the sequence, and we found a region where the degeneracy of the code was limited. I'll come to the explanation in a second. As soon as we had the amino sequence, we called up the people back home who started to synthesize an hour later. I think the next

5. See the oral history in this series with David Goeddel.

day we were already furiously screening our libraries in hope to find the interferon. That was definitely an intense moment.

Hughes: Who revealed the sequence?

Heyneker: I think it was somebody from DuPont. I forget. I know that Dave Goeddel will remember this exactly.

Anyway, if you want to make probes based only on the amino acid sequence, what you are looking for are regions in the amino acid code where the degeneracy is as low as possible. For instance, there are six codons which code for serine; there's only one code for tryptophan. So we looked for anything that had a tryptophan or a methionine in it, which is also a unique codon, or let's say amino acids for which there were only two codons. Those were regions which were particularly interesting because only a limited number of probes would encompass certain amino acid sequences. If the amino acid sequence was truly degenerate, we would pick up all sorts of false positives. Or we had to make too many probes, and it would become very difficult to do, very cluttered. Normally we need around five amino acids, because five amino acids, five times three, is fifteen nucleotides. That is specific enough to initiate a search using this hybridization technique.

Hughes: Was this common knowledge?

Heyneker: No, we developed it. Well, I think that it was common knowledge that this could be an approach which could work, but there were not many examples that it should work. We at Genentech were pioneering this. But I don't want to go so far as to say that it was all our idea and no one in the world knew about it.

Hughes: Was it apparent to the presenter that the sequence information was important and that people like you were going to seize it?

Heyneker: I'm convinced of that. As a matter of fact, probably for that reason, I don't think that the entire sequence was shown. But still we got enough information to go forward.

Hughes: Which may indicate that the way you were doing it wasn't broadly known.

Heyneker: Possible. That's a good point.

Hughes: Otherwise, one would think that the presenter would have been more careful.

Heyneker: Maybe. You should discuss that with Dave Goeddel, who really led this interferon project.

Well, going on, we entered into collaboration with Hoffmann-LaRoche, and they also had some information on the sequence. As a matter of fact, I might have been confused. It might well be that Roche presented the amino acid sequence data, and that later we got together with Roche and closed the loop. But anyway, we further developed the interferon with Hoffmann-LaRoche. Eventually, we managed to express the interferon, especially when we developed the tryp promoter system which was a stronger expression system. After making some changes in the beginning and the end of the insulin construct

over time, we managed to improve the yield of interferon expressed in *E. coli* significantly.

Discovering Multiple Interferons

Hughes: You're talking generically about interferon. Is that because—

Heyneker: That's the way it started. I think that it is a very good question. We learned that there were more interferons. It turned out that there was a whole family of alpha interferons, and there was also a beta interferon, and we later worked on a gamma interferon. So it became a much bigger project.

Hughes: Was Genentech the discoverer of these new families?

Heyneker: I can't recall. I think to a certain extent yes. It turned out that what we cloned was an alpha interferon of the alpha family. Having this entire sequence, it was quite easy to pull out related sequences. We pulled out a whole bunch of related interferons.

Hughes: Yes, you did. By 1982, Goeddel had cloned eight interferon genes, including interferon gamma, which was the one that people were not even sure existed.

Heyneker: That's correct. But interferon gamma is not that closely related to interferon alpha, so that's why it has a special name.

Hughes: And the same with beta?

Heyneker: And the same with beta. It was a truly unique property of interferon alpha that it was part of a family of related genes. Both of the genes that Goeddel et al. pulled out were alpha interferon genes. We had a separate effort on beta interferon and a separate effort on gamma interferon, and they were all successful: We cloned them all.

The alpha interferon story gave us the opportunity to mix and match, to have a front part of an alpha interferon A with a back part of alpha interferon D. So you could make all sorts of interferon combinations which were not natural. It was very interesting to see if those interferons still had biological activity or enhanced biological activity or different properties in general. So that by itself from a scientific point of view was quite interesting. It was the beginnings of gene shuffling.

High Expectations

Hughes: Yet the interferons were initially a bit of a disappointment in terms of their therapeutic use. There had been a tremendous amount of hype about their potential in cancer and viral disease therapy.

Heyneker: That is a very interesting observation. Yes, in the beginning, it was all hype, but currently it is a billion-dollar product, and there is no other billion-dollar product at Genentech. It is four times bigger than tPA, and it is four times bigger than human growth hormone. Perhaps Genentech is playing it down, but it was a roaring success, compared to the products that Genentech ended up with.

Hughes: Interferon was supposed to be—

Heyneker: Magic.

Hughes: —a miracle.

Heyneker: Absolutely. The expectations were incredibly high. That was due to our true ignorance of the biology and immunology of these cytokines and growth factors, et cetera.

Hughes: "Our" meaning science in general?

Heyneker: Absolutely. There was an interferon society of people who had minute quantities of interferon and were claiming all sorts of incredible results. But once we had cloned and had larger amounts of it, we understood that it's not a cure-all, and that it was definitely part of a natural defense mechanism in higher eukaryotes. So, I agree with you; it was definitely hyped up. At the same time, it was a highly successful product, developed and marketed by Hoffmann-LaRoche for certain cancers and I think also for hepatitis C now, which is a big application.

Competition

Hughes: Interferon was the basis upon which Biogen was founded. How aware were you of the competitiveness of this area?

Heyneker: Oh, you mean the cloning aspect. That was incredibly competitive. That's why we were writing down the amino acid sequence and the same afternoon we were screening. We were aware that it was incredibly competitive. If we could make interferon, not knowing that there were all of these classes of molecules, we thought that we would be forever happy and independently wealthy.

Hughes: Which happened anyway, but not quite the way originally envisioned. [laughs]

Heyneker: That depends on the definition. [chuckles]

Hoffmann-La Roche

Hughes: Please comment on Genentech's relationship with Roche, including with Sidney Pestka, in terms of interferon.

Heyneker: It was competitive between the Genentech and Hoffmann-La Roche groups. We were young and the tension and the expectation was high, and we all wanted to get part of the glory. I think that the relationship with Roche was a love-hate relationship. But it was quite healthy, and at the end of the day they were a very good partner for Genentech.

Hughes: Did you have interactions with the Roche people?

Heyneker: Definitely. I went to quite a few meetings in Nutley, New Jersey, and also they came to Genentech. Products like tPA and human growth hormone we developed for our own in-house use, therefore manufacturing it and selling it ourselves. It was very important for Genentech to keep a few winners, and alpha interferon was not part of it. There were others, like factor 8 we completely licensed out. Most of the products we licensed out.

Hughes: Why?

Heyneker: To raise money.

Hughes: Was it also a matter of manpower? How many things could you work on at once?

Heyneker: Yes. We also had to build an infrastructure that we could bring products to the market ourselves, which takes time. With alpha interferon, it was clear that Roche was the partner to bring it to market.

Hughes: Well, that was early in Genentech's history.

Heyneker: Exactly. Although, at the same time, Bob Swanson, rightly so, wanted to build Genentech into a fully integrated pharmaceutical company. I think that it was probably with some pain that he let go of these products.

Genentech's Vaccine Program

Hepatitis B

Heyneker: Genentech made also its share of mistakes in letting go products. For instance, we had developed around that time a very interesting vaccine against hepatitis B, which we did not develop ourselves, and which we wanted to partner with another company. I think that Genentech absolutely made a huge mistake by not either developing it in-house or finding the right partner to develop it collectively, because it turned out to be another billion-dollar-plus product.

Hughes: Wasn't that pretty obvious at that time?

Heyneker: To certain people it was very obvious, but not to business development and not to Bob Swanson.

Hughes: That surprises me because hepatitis B was rampant—

Heyneker: In Asia. It still is.

Hughes: And in certain communities in this country as well.

Heyneker: Yes. Well, it was Bob Swanson's position that we should not touch vaccines because of the liability associated with them. My counter argument was that [through recombinant DNA technology] you could express one protein and not the entire virus. Here you have the opportunity to have a much much safer product because you could never create a viral infection with it. That was theoretically impossible.

Hughes: Others, such as William J. Rutter, certainly believed that.

Heyneker: We were competitive enough that I saw other people basically benefit from it, while we had clearly a superior product.

Hughes: Is that so?

Heyneker: There's no question about it. The way we made it and expressed it, it was highly immunogenic, and I think that it was a fantastic product.

Hughes: What happened? Was it shelved?

Heyneker: No, I think we partnered with SmithKline, but they never became a serious player. We offered it at an exorbitant price to Merck, and Merck said, "Look, at that price we will develop it ourselves," and they went with Chiron.

Hindsight is easy, but the reason why I bring it up here is that I had heated discussions with the business development group and others about this, and I think that they were wrong, and they were wrong in too many other cases, which made me quite bitter. I think that Genentech could be a significantly bigger company had we kept the right products for ourselves or had developed the right products.

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Hughes: Business development was Bob Byrnes?

Heyneker: Yes, Bob Byrnes, and then later Jim Gower.

Hughes: Had they had experience in developing pharmaceuticals?

Heyneker: Bob Byrnes? No.

Hughes: Was that maybe the problem?

Heyneker: May well be. Bob Byrnes, I think, was wrong about the hepatitis B program. Genentech was wrong in general that they did not pursue the vaccine program more vigorously. We had hired Obijeski to head that effort, and it became really a serious disappointment because we had all sorts of interesting projects which were going nowhere. I thought

vaccines were low-hanging fruit to be picked, and here was an opportunity to develop vaccines which were safe and efficacious.

Hughes: And other people did. [laughs]

Heyneker: Don't rub it in. [laughter]

Hughes: Dennis Kleid said that he too was upset about lack of support for the vaccine program.[6]

Heyneker: Absolutely.

An Aborted Project on Malaria

Heyneker: Well, since we are venting some personal issues, which are probably good to put in writing anyway, I had also a project developed on malaria very early on. I had forged a collaboration with Huth Neussenzweig at NYU, and at that time she was definitely, in the United States, an authority on malaria. Here I saw an opportunity to learn something more about the disease and do some cloning. It was a very sexy subject. Perhaps we were a little naïve, but we thought, here is another opportunity to make a vaccine against a serious disease. It turned out later that a malaria vaccine is quite complicated. So in hindsight, we probably would not have been successful. But, as long as you don't know that, here was again a significant opportunity.

That collaboration came to a very unfortunate end. One Saturday I was talking to Tom Kiley. Tom Kiley introduced me to a new hire. It was Brian Cunningham as the new legal counsel at Genentech. So after this introduction, we started to talk about what I was doing at Genentech. So I mentioned a few things, among them my interest in malaria. Tom Kiley quizzed me about it a little bit and said, "Perhaps we should not do vaccines." I said, "Well, it is a great opportunity." Which is fine—I think a dialogue should go on. But then Brian Cunningham, being on board a couple of hours at Genentech, said that we should not continue this project. I never got over that. Somebody who just came on board is going to tell me what to do? That really killed me. I was so angry. Yes, that was really the beginning of my disenchantment.

Hughes: Did you confront him?

Heyneker: Of course. I asked where he was coming from. I'm emotional so that doesn't help. Therefore, I've never been close with Cunningham, although I think that he is a nice guy and so on. But that just rubbed me the wrong way, and I did not recover from it.

Hughes: I can understand. I can think of at least two reasons why a businessperson might be skeptical of vaccines. After the Cutter polio vaccine debacle in the 1950s, many of the big pharmaceutical companies stopped manufacturing vaccines because of the liability problem.

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6. See the oral history in this series with Dennis Kleid.

Heyneker: Yes, but that is the argument why recombinant vaccines overcome this problem.

Hughes: Exactly. Another argument used against vaccines was that they weren't very profitable. For example a malarial vaccine would be mainly useful in the developing world.

Heyneker: Those things were mentioned by Kiley and Cunningham. Of course, they are right from that point of view. But I felt that it was so inexpensive to bring that concept one step further. You can sell it back to the World Health Organization or whatever. But the cost of developing a product in the research phase is minimal compared to manufacturing and sales. We were so much in the beginning of the costs associated with development of the product that it didn't matter that much. That was my view, and it is still my view. You get patentability. There's a lot you can do without developing your product further. But bring it to the stage where somebody else can pick it up.

Hughes: There's also the argument that malaria is at the top of the list of infectious diseases killing the most people in the world.

Heyneker: Over a million a year. And a much larger number is infected per year. You preach to the choir.

Hughes: I know.

Heyneker: Anyway, that was definitely something which made me unhappy.

Protein Expression Systems

Hughes: Let me ask you one more thing about interferon. You had tried to express hepatitis B in the yeast system?

Heyneker: We tried it in a mammalian expression system and/or bacterial. Larry Lasky was in charge of the project.

Hughes: Do you know how the expression worked?

Heyneker: Fantastic, incredible, very high levels of expression, very antigenic, great project—much better than the yeast product.

Hughes: And yet the yeast system was used to express the interferons, wasn't it?

Heyneker: I think we really focused on bacterial expression and mammalian cell expression. Yes, we did work on yeast expression, but it was not really one of our mainstream development efforts.

Hughes: Are *E. coli* systems, yeast expression systems, and mammalian cell expression systems all very different, requiring different people to manipulate them?

Heyneker: No. For plasmid construction or construction of other vehicles to get the foreign DNA into mammalian cells or yeast cells or bacterial cells, the molecular biology was all quite similar, although you need different expression vehicles and that sort of stuff. It was more the tissue culture knowledge which we molecular biologists often didn't have. It came more out of the cell biology field.

Hughes: Is that what Art Levinson brought to Genentech?

Heyneker: Yes. [tape interruption]

The Urokinase and Tissue Plasminogen Activator Projects

Collaboration with Grunenthal

Hughes: Here is a subject that I think you are quite eager to talk about, namely urokinase. Whose idea was it to work on urokinase? [tape interruption]

Heyneker: Well, the urokinase project was introduced to me through Grunenthal, a German pharmaceutical company. It was a deal between Genentech and Grunenthal to clone the urokinase gene in a collaborative effort—basically market the product as an end result. It was a very interesting project, and I was quite excited about it. Bill Holmes, my research associate—very capable—ran with the project. It was really his project to do. It was very challenging, and I think that he was the right guy to carry it out.

Hughes: Why was it challenging?

Heyneker: There was not that much known about urokinase. There were some amino acid sequences known, and based on amino acid sequences, we had to find regions where the probe was not very degenerated, and therefore there were not many different probes. Part of the project was being carried out by Grunenthal which had access to small amounts of pure urokinase material.

The interesting part of such a project is that you don't have results till you have a clone. It is very difficult to measure progress in such a project. That became very obvious when Grunenthal asked for an update on the project. Bill Holmes had been working on it furiously for half a year to a year, making cDNA libraries and probing these libraries with degenerate probes. We found clones which looked a little bit more positive than the others—the results were not clear cut. Every time we found a clone, we needed to confirm it by sequencing. Most often, the clones we found turned out to be false positives. Therefore the sequence didn't match. So, it was very frustrating and very tedious. We had to go through thousands and thousands of clones, which we had to pick individually with a toothpick and put these clones in a ninety-six microtiter plate in each position so that we could have these libraries we could go back to. So, it was a lot of work, but not a type of work where you could show progress.

Genentech Scientists, Pajaro Dunes, California, September 1982. Left to right: Dennis Kleid, Dave Goeddel, Art Levinson, Herb Heyneker, Peter Seeburg, Dick Lawn, Axel Ullrich.

photo courtesy of Herbert L. Heyneker

I recall clearly that Grunenthal came by for an update, and I had to give the update, and I had no clue what to say. The answer was very quick: "We don't have it yet." They were paying good money to Genentech for this privilege, and they were not amused when the scientific part of the meeting was done in five minutes. So, I don't think I was very popular with the management which had to assure Grunenthal that they were not wasting their money. At the same time, that was the situation. We tried hard and we didn't get the clone.

A Cloning Success

Heyneker: I was on a trip in New York—I still remember it like the day was yesterday—and on Saturday morning there was a telegram or a message. Bill Holmes wrote, "UK in the bag." It took me a while, "UK in the bag?" All of a sudden it dawned on me, "UK" of course is urokinase, and "in the bag" means we have it. I was literally jumping up and down in bed because this was something that we had been waiting for for close to a year. Here's the good news. Once you confirm the clone by sequencing, you know for sure that it is the right clone, because all of a sudden, based on the DNA sequence, you can now translate it to the amino acid sequence. Here you saw one amino acid after another fitting exactly with the strings of amino acid sequence done by the people at Grunenthal. So it is a total "yes" answer. So once you have it, you have it. So from then on, the project went significantly better, and the relationship with the people at Grunenthal cleared up, literally overnight.

I have to say that Leopold Flohe who was the project leader at Grunenthal understood it and was very supportive in general. The people there doing the work on the protein biochemistry part of this urokinase project were very supportive as well. It is wonderful when you all of a sudden see this whole molecule unfold for you, and it turns out to be a very exciting molecule. We recognized that there was a serine protease region, which you expect because it isn't a protease which cleaves the fibrin clot. Also, there was a domain on this protein which was a binding domain, so-called kringle. This binding domain would direct this enzyme to the right position. So all of a sudden it was an interesting, exciting molecule, and all sorts of pieces of the puzzle fell right into place.

Abbott Claims Urokinase

Heyneker: Well, we decided to publicize that effectively we had cloned the urokinase gene, and we wanted to do that in Japan. There was an international conference on biotechnology in Kyoto, and we knew that there was another paper on cloning of urokinase by somebody from Abbott. We felt it was particularly interesting to present our work there and see what the competition had to say. We were one hundred percent confident that what we had was correct. There was zero chance for a mistake, so we presented the data without showing the DNA sequence, because we kept that for ourselves; it was too proprietary. We gave this picture of what the molecule looked like, that there was this serine protease

and kringle part to it. So we could tell a nice story. Also, we let the audience know that the protein sequence and the DNA sequence were perfectly in sync with each other.

Dr. Huang from Abbott gave a presentation which preceded my presentation. He was sort of hand waving that he had cloned urokinase. He showed some data which were very weak and did not correlate at all with our data. I remember that I started my presentation by saying that I didn't know what he had cloned, but that I was convinced that it was not urokinase. [laughter] We were quite competitive in those days.

Hughes: How did the audience react?

Heyneker: Everybody was laughing.

Hughes: Except Dr. Huang.

Heyneker: Probably not. But interestingly enough that did not stop Abbott from suing Genentech that Abbott was first to clone and that they wanted to have access to the clone. There were terrible negotiations and terrible depositions and fact-finding missions about who cloned what first, and they never cloned it. When we asked for that clone, they said, "We lost the clone, but we did clone it." It went on and on; they were so persistent, and Genentech had lost a little bit of interest in urokinase. I think that this lawsuit was settled and that Abbott could continue their work on urokinase. Here was another example of a big company muscling their way in. They had absolutely not cloned the urokinase gene. I can say that with my hand on my heart. But they got their way. Genentech basically gave in, something which I absolutely disliked, because it was a matter of honor almost that we had that clone. Abbott was all false and malicious and knowingly lying. But what can you do? So, that was a very unfortunate situation.

Comparing Urokinase and tPA

Hughes: Was the reason for settling in the end because Genentech had decided to focus on tPA rather than urokinase?

Heyneker: Correct. I think that tPA had more interesting properties than urokinase.

Hughes: It was a money decision, not a moral decision?

Heyneker: Correct. I did very well understand that Genentech had to choose and that the choice was tPA. It made a lot of sense, because we did not have to share it with Grunenthal. So we let Grunenthal develop urokinase, and I think they did. I think that Grunenthal is even selling the product on the market.

Hughes: To treat blood clots?

Heyneker: That is correct.

Hughes: Is tPA the superior product?

Heyneker: I think at the end of the day it is slightly superior. Interestingly enough, when you compare the urokinase and tPA molecules, both are serine proteases, very related. Urokinase has one kringle region and tPA has two kringle regions. I mentioned to you that these kringle regions are involved in binding to fibrin. So it might well be that tPA has a higher affinity for fibrin, and therefore higher specificity for clots. Also, we confirmed that we had cloned tPA several weeks before we had confirmed that we cloned urokinase. Within a couple of weeks, we obtained a lot of information on these molecules. I did not care that we chose to continue on tPA; that was fine with me. I think that we had successfully finished the project, and we had successfully handed it over to Grunenthal. It would be much more disappointing if we had cloned tPA and I was unable—or my lab was unable—to clone urokinase. But again I would say that Bill Holmes did an outstanding job in doing that.

Hughes: He sounds like a very tenacious individual.

Heyneker: Yes, he is a very interesting character. He never went to the hairdresser after the age of fourteen, and we always threatened to him that in his sleep we would cut his hair off. That was the one thing that he could not even joke about, it was so sacred. He is a good-looking guy with this long, long hair, so he was definitely eccentric, but he was very smart.

An interesting story which probably leads very nicely into the tPA project is that Désiré Collen, who was starting to collaborate with Genentech on the tPA program, spent one summer in my lab to learn molecular biology and cloning. He spent an enormous amount of time with Bill Holmes, myself, and Gregory Gray, and he had a great time. It was absolutely fantastic how here this established professor from the University of Louvain fit in with a bunch of wild guys to learn the ins and outs of cloning. He was very good at it and a very good sport. It tells you what an interesting character Désiré Collen is that, as an M.D. and doing all sorts of other stuff, he wanted to have hands-on experience. He took a sabbatical for four months and stayed in my lab, and we had a fantastic time.

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Heyneker: Bill Holmes went to Désiré Collen's lab for two years, and he received his Ph.D., which I found very interesting that somebody from America went to Belgium. There are a lot of Europeans who come to the States to study here, but it's not what you call a two-way street. I must say it was very impressive that Bill did this and successfully obtained his Ph.D. there.

Hughes: And came back here?

Heyneker: And then came back.

Research Strategy and Style in the Heyneker Lab

Désiré Collen

[Interview 8: May 22, 2002]##

Hughes: You mentioned last time that Désiré Collen was in your laboratory for one summer and how successful that visit was. Was there a connection between that visit and the work on tPA that ensued?

Heyneker: Absolutely. By the time Désiré Collen visited my lab, we had already started on the tPA project. Désiré wanted to understand what it entails to clone a gene like that to get a better appreciation for the challenges of a project in those days. I must say I was always very impressed with Désiré. He was an extremely driven scientist, a good organizer. He has a big lab in Belgium, but he is humble enough to try his hands at something new. In my lab, especially with Bill Holmes who was eccentric to say the least, I think it was an eye opener for Désiré how we as molecular biologists were conducting our experiments. He was a highly respected professor in Belgium. He was thrown into the trenches and had to participate in a unique way of doing business, getting molecular biology explained by Bill Holmes and by me. It was definitely a different experience, but he loved it. He rose to the occasion—or maybe sank to the occasion—but we had such a great time. He managed to become truly part of the lab in very short order.

Hughes: Was he used to doing hands-on science at that stage of his career?

Heyneker: Well, I don't think as much, but it was clear that he had relevant experience—he picked up things very quickly. He was in Belgium no longer a bench scientist; he was more directing the research.

Hughes: The unconventional way in which Genentech operated in those days was not the way he was used to conducting research?

Heyneker: I don't think many people were used to this, but it was infectious. It was very relaxed on the one hand, but there was a lot of pressure to do it quickly, to do it right, to be the first. We had an enormous sense of getting there first and making Genentech the premier company. It was an art. That is the best way to describe it. We tried to be artists. When you are in front of your painting, it is very important to do the right brush strokes in a very particular way. I mentioned it already with urokinase: the problem with cloning is you haven't cloned a gene until you have cloned it. You cannot be a little bit pregnant. It is a yes or no answer. You could search a long time in those days with these synthetic oligonucleotides. It was definitely a challenging method to fish out particular genes. You had to get used to it that you were not making progress on a daily basis. If it was a big experiment, you did a transformation; you picked literally thousands and thousands of clones. They were picked one by one with a toothpick that we poked into a bacterial colony, and then we put that toothpick in a ninety-six well microtiter plate, so we could do ninety-six colonies per plate. And we had stacks and stacks of plates. That became a

library. So, it was a lot of work, and a lot of the work was not very intelligent, but it had to be done. So you take turns and everybody participates.

Searching for Specific Genes

Heyneker: What was novel was that in molecular biology then, we were feeling our way. It was a lot of handwork. When we had a new cDNA library, we always started very enthusiastically, and then performed hard work to build the library, and then hybridized synthetic oligonucleotides to it in the hope that specific colonies would light up. Inevitably, lots of colonies would light up a little bit, so there were a lot of false positives: what is the real one? What is not the real one? So, a lot of sequencing had to be done. But at one point in time you get the right thing, and then it is absolute euphoria. I always like to compare this type of endeavor with mountaineering. You go to deep valleys to scale the next peak and once you are on top, once you have the clone, you have a fantastic view everywhere. That's why you do your mountaineering—to get to the top, to the view. But eventually you have to descend again to scale another peak, and the valleys can be pretty long and deep and dark.

Hughes: I get the impression that you found this true of molecular biology rather than biology as a whole. Why would that be?

Heyneker: Because it is searching for the needle in the haystack. With most research you make slow progress, experiment by experiment, until you get a picture of what is going on. That is the detective work—to do the right work to prove a hypothesis. Here [with the libraries], it was more like you don't have to be particularly smart, but you have to get organized and do it. Your jollies come later once you have the gene cloned and sequenced. All of a sudden you are overwhelmed with an enormous amount of information. Once you find the diamond in the rough, you can enjoy that gem and really learn a lot.

Hughes: Conceptually, it was very straightforward, wasn't it? You were trying to isolate and clone the gene. The Genentech group had a huge role in refining that technology. Is that where the creativity came in?

Heyneker: That is exactly right. To a large extent we were writing the book on these things. In hindsight, talking about this now, it all looks easy and straightforward. But in those days we didn't know for sure if this was the proper way to get your clones. We thought so, and in the end we were right. But if you go through long dry spells before you find your next clone, this is a little nailbiting because you don't know the future; you don't know if you will succeed. Genentech was very good using synthetic DNA for all sorts of research to make things happen. Finding the right clone, again we used synthetic DNA to fish it out. We used synthetic DNA to express the genes. So we had this experience in that area.

Combining Synthetic and cDNA Approaches

Hughes: We're talking I suppose about the very early eighties if we are talking about tPA. We've talked before about how there were only a few other groups that had synthetic DNA capacity. So what were people without synthetic DNA capacity doing? How were they making their clones?

Heyneker: By the early eighties, synthetic DNA became much more accepted and an important tool. Genentech had an advantage that we were first and we pioneered this. We took advantage of that. But I think that by the eighties synthetic DNA became the tool everybody was using. It's always hard to stay ahead of the game. To play catch-up is much easier than to stay ahead. I'm not trying to say here that we invented synthetic DNA—not at all. [Gobind] Khorana and others were working on this for a long time, and they deserve a lot of credit. Our strength was to combine the synthetic DNA approach with the natural cDNA approach and to utilize it.

Hughes: Was anybody else doing that in the late seventies?

Heyneker: Perhaps a few groups, but it was not widespread at all.

Differences in Personal Research Styles

Hughes: You told me that Collen came to learn recombinant DNA.

Heyneker: Correct.

Hughes: And DNA synthesis?

Heyneker: No. I think his goal was to learn the techniques and bring back the techniques to Belgium. When Désiré was there, Diane Pennica[7]—as far as I can recall—was still in my lab. Thereafter, she went to Goeddel's lab and continued to do tPA. There was a lot of work, and we split the work up. So my lab focused on urokinase, and Dave Goeddel's lab focused on tPA.

Hughes: It was a lot of work because the gene was a needle in a haystack and required a lot of work to pull out?

Heyneker: Exactly, and Dave Goeddel was particularly good at finding needles in haystacks. He was relentless. He would build one library after the other. He was sure that he would find it, and he did on many occasions. That was one of Dave's strengths.

Hughes: Were you less confident that you would find it?

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7. See the oral history in this series with Diane Pennica.

Heyneker: Well, our approach was slightly different. I liked little experiments to see if I could prove something, or if I could change something. That's why I was particularly happy that I was focusing on those promoter studies because I didn't have to grind down one library after another. I needed a little bit more creativity. I think that Dave Goeddel was incredibly creative, so don't get me wrong. But he had the tenacity to really go for it. I was probably less tenacious. Bill Holmes seemed less tenacious, but knowing him well, he was very tenacious. He had a very clever way of hiding it. But I think he was just as driven to get his clone. There was still a lot of personal glory to be had, and as a scientist if you could assign a paper to your name that was very important for your career.

Hughes: Was it so in industry? I can see how number of publications and where they were published would mean a lot to your academic colleagues, but in terms of getting ahead at Genentech, did it make any difference?

Heyneker: Maybe. If you are prolific and do good work, that is of course noticed. There is definitely a correlation between productivity and moving up the ladder or getting monetary rewards or whatever. There were definitely incentives to be good, and it should be that way.

Hughes: So the push to publish, which is a strong urge in academia, was not as—

Heyneker: —as strong. It was still desirable. I often lost the interest once I had it cloned. When I knew what the answer was, I wanted to move on and do something else. I was always a good starter but not particularly a good finisher. Luckily enough, there were always a lot of people who are good to dot the i's and cross the t's and fill in the blanks.

There are two types of science if you go to the extremes: on the one hand a scientist would like to push the frontiers of science and truly come up with some novel things. That creates a patchwork. There's just as important a science to fill in the patchwork, to make sure that it all correlates and fits together. So it's truly a puzzle that you finish. If I have to characterize myself, I was much better at pushing the frontiers than filling in the blanks, although I realized how important that is. If you don't do that, you can easily get on the wrong track without knowing it for a while. That's why it is good to do your science in a group and make sure that together you cover the bases.

Hughes: Taking advantage of everybody's strengths?

Heyneker: Yes, I think so. I think that Bill Holmes also likes to push the frontiers more than filling in.

Hughes: It seems to me that this could also explain your comment of last session that writing a paper was not a top priority.

Heyneker: Well, I am particularly bad at it. That is probably the main reason. [tape interruption]

More on Tissue Plasminogen Activator

Comparing Urokinase and tPA

Heyneker: I want to say a few more things about Désiré's visit to my lab, because it definitely had a lasting impression. We became very good friends, and I still remember that before he left, the lab took him on an outing in San Francisco. After a nice meal in North Beach, we found a place on Fisherman's Wharf where you could dress up. We decided to dress up in wonderful medieval dresses. A picture was made of the people in my lab with Désiré, which was absolutely wonderful, the most hilarious picture I have seen in my scientific career. I will dig it up and put it in the records of this oral history. It was a great goodbye to Désiré—very memorable. I am flattered that a guy of his stature wanted to learn a few things in my lab.

Hughes: Did he continue to use what he had learned in your lab?

Heyneker: Absolutely, he definitely built the same capability in his lab.

Hughes: Did you know, and did you care to know, how tPA works biologically?

Heyneker: I remember that it was very interesting to see the similarities and differences between the urokinase gene that my lab cloned and the gene that Dave Goeddel's lab cloned. There were incredible similarities and differences. As I mentioned last time, the similarity was, they were both serine proteases—very similar in structure. Urokinase had one kringle, which is a protein domain, associated with binding to fibrin, and tPA happened to have two of those kringle domains in tandem.

Hughes: Did you immediately deduce that tPA was going to bind tighter?

Heyneker: That is why we felt that tPA was a better candidate to become a drug, because it had this probably tighter domain. If that is true in the long run, I do not know. It takes a lot of work to determine that. These molecules build modularly, kringle domains followed by a protease domain. What it meant was that in the bloodstream or wherever it was made it was meant to bind somewhere and act. Only in those places was it meant to do its work.

There were other reasons why we chose tPA. There were business reasons; there were proprietary reasons. We had a better chance of building them; a patent portfolio built around it; we might have had more ownership of the molecule than of urokinase. Also, this technical revelation that it had two kringles instead of one. A lot of those issues were probably payrolled for Genentech to place its bet on tPA. And I think it was the right bet.

Hughes: In the past, the way drugs were tested was usually through animal experiments. You inject it or you feed it or whatever, and then you see what happens on a macro scale. Is the revolution happening at Genentech that you were approaching function from the molecular level?

Heyneker: To a certain extent, yes. However, we are always surprised by animal studies. They are not a logical extension. I think they are suggestive. I would not bet that it will work as predicted in an in vivo situation. There are too many examples of people being surprised by in vivo data versus in vitro data.

Hughes: That is a realization that you have had from the start?

Heyneker: No, I am not at all a pharmacologist. I was probably just as surprised as other people if something like that would happen. We knew from the studies Désiré Collen did early on with natural tPA that it was quite an exciting molecule. When we cloned it and we could express it, we were pretty sure that it would have biological activity.

Biological Activity of the First Recombinant Insulin

Hughes: The issue of biological activity makes me think of the criticism leveled at the insulin work, I suppose from those with a biological orientation as opposed to a molecular orientation: "Yes, you cloned and expressed it, but you haven't proved that your insulin is biologically active." The criticism seems to me to point out differing scientific discipline perspectives.

Heyneker: Yes and no. The problem with insulin was that nature makes insulin as proinsulin. It makes it in the form of a single-chain insulin that has the alpha and beta domains which are connected by a C-peptide.

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Heyneker: When we started with an A-chain and a B-chain, and we tried to refold them, there was no precedent to suggest that they would fold exactly the same way they would fold starting from the proinsulin form. So, there definitely was some room to challenge our approach.

Hughes: When I asked Dave Goeddel a similar question, he said something to the effect: To a molecular biologist, if you express a protein, sequence it, and the sequence correlates with the sequence of insulin, that is enough for a molecular biologist. I may be doing him a disservice. His answer was probably more complicated than that.

Heyneker: For a molecular biologist, we are happy if the gene correlates with the protein sequence—that's the first line of proof. But people like Ron Wetzel and Mike Ross, who were certified protein chemists, realized that there was more to it. The three-dimensional structure of a protein determines its biological activity and not just the linear sequence of amino acids.

Hughes: But those two didn't come to Genentech right away.

Heyneker: By the time that we were doing tPA, we had quite an extensive protein biochemistry group. Even with insulin, we had Ron Wetzel on board to demonstrate biological activity. It's not that we were ignorant or that cloning and expression were sufficient for us. We

realized that it was necessary to bring protein biochemistry on board to take the technology to the next level.

Hughes: Was biological activity associated with how the protein folded by the time you were doing the insulin work?

Heyneker: Yes, absolutely. I would say that lots of work was done on trying to elucidate three-dimensional structure through x-ray crystallography—

Hughes: Yes, in the thirties. By Max Perutz, for example. Did those people correlate three-dimensional structure with biological activity?

Heyneker: I would say yes, absolutely.

Continuing the tPA Story

Competition and High Expectations

Hughes: TPA as you well know is an enormous molecule, by far larger than anything Genentech had worked with before. Were there particular problems because the molecule was so large?

Heyneker: We knew that the molecule was large when we started the project. What surprised us probably more than anything else is that it has an enormously long 3-prime untranslated region. Once we cloned it, we found out that around 800 to 1,000 nucleotides were all devoted to an untranslated region. That was definitely unexpected.

Hughes: What is the significance?

Heyneker: We don't know. It might have to do with specificity of expression, but I am now using the knowledge of the year 2002. When we cloned tPA and found this out, I don't think that it was appreciated what those noncoding sequences were doing.

Hughes: Who were Genentech's competitors in tPA? There were a lot eventually.

Heyneker: Yes, I think so.

Well, I know that I had competition with urokinase cloning, and I mentioned the sad story of Paul Huang from Abbott who also claimed that he cloned it. There was also this person from Belgium, Bollen, who claimed that he cloned it. We were very confident that we were absolutely the first to clone urokinase. In the case of tPA, we were pretty convinced that we were the first.

Hughes: TPA is a bit like interferon: there was a tremendous amount of expectation of what these drugs were eventually going to become for various companies. And tPA didn't initially pan out that way. Why was market share inaccurately predicted for tPA?

Heyneker: I don't know. I'm not a business development guy, but I do remember that I was very upset about it.

Hughes: Why?

Heyneker: Perhaps in my naivete, I thought and still think that it could have been done better.

Hughes: Give me a clue about what you are thinking.

Heyneker: Well, Genentech made known to the world that tPA was a billion-dollar drug, and to see it stall around a hundred and fifty million is not a factor of two but a factor of seven lower than predicted. And that surprised me very much.

Hughes: What were the predictions based on, to go so wrong?

Heyneker: To be really honest, I don't know.

Hughes: In 1987 there were nineteen companies working on tPA. I got that from an article in *Nature* published on July 16, 1987. I wonder if there were many more competing drugs than Genentech originally anticipated.

Heyneker: There were two competitors: there was urokinase and there was streptokinase.

Hughes: Beecham had a tPA called Eminase. And there may have been other competing drugs. Maybe the competition was not so clear when these market projections were being made.

Heyneker: I think that market acceptance and market introduction were slower than projected. We charged a very high price, which caused quite a bit of resentment, rightly or wrongly. I think that the price we were charging was okay because tPA saves days in the hospital setting. Streptokinase, which was much cheaper, therefore had a chance to make inroads.

Hughes: Streptokinase was <u>much</u> cheaper. Wasn't it something like $200 per dose, while tPA was something like $2000?

Heyneker: Yes, but at the same time streptokinase is antigenic, which means that if you need it more than once, the chances of severe immune reactions are significant. So is the difference of $1800 worth worrying about? I doubt it.

Hughes: Not to the individual, maybe to a hospital system.

Heyneker: Yes. Again, I'm not a business development guy, so I shouldn't say much, except that I was absolutely surprised that we could be that far off in our market projection to the extent that Genentech needed to be rescued.

Hughes: By Roche?

Heyneker: Yes.

Hughes: How did you keep in touch with work at Genentech after you left?

Heyneker: Through colleagues. Listen, I never thought of myself as leaving Genentech and being in a different company. I always thought that I was going into a joint venture of Genentech—a friendly joint venture—and that I was still a part of the family. I always tried to keep up with Genentech.

The Burroughs Wellcome Lawsuit, London, 1987

Hughes: An article in *Science* in 1987 stated that at the time tPA was being developed, only Genentech and Burroughs Wellcome, which were the two litigants, had the technical know-how to grow mammalian cells in large volume.

Heyneker: I doubt it.

Hughes: It was pretty late; it was 1987.

Heyneker: That's pretty early, too. Well, what is significant about this is that the original premise was that you could make a limitless supply of proteins by expressing and producing them in bacteria. Then it turned out that it is not always so easy to express mammalian proteins in bacteria—there's a lot going on that is probably not in sync with the bacterial machinery. So I think that Genentech made the right decision at the right time to also investigate mammalian expression systems.

Hughes: Which I associate, as we mentioned last time, with Art Levinson.

Heyneker: Absolutely.

Hughes: Who came to Genentech pretty early. So, maybe by 1987 mammalian cell culture had been going on at Genentech for eight years or so?

Heyneker: I don't know if we hired Art Levinson to develop mammalian expression systems. I think we hired him because he is a very smart guy.

Hughes: That could be. But don't Chinese hamster ovary cells as a culture medium come into play with interferon?

Heyneker: Sure. Well, I'm on thin ice here. I doubt if Genentech was the only visionary to know anything about large-scale mammalian cell cultures. To use mammalian cells for expression of recombinant DNA products—that's a different story. I must say that I think that Genentech and Burroughs Wellcome were probably pioneers in that area, but I don't think that they developed large-scale tissue culture.

Hughes: Burroughs Wellcome contested the patent from the standpoint that the technology was obvious; anyone with knowledge of the art could do this. Therefore, they maintained the

patent was invalid. They had people like Tom Maniatis saying that, and Paul Berg contradicting on the Genentech side.

Heyneker: The case has much more to do with patent law and how patent laws are interpreted than with anything else. It's an example of extremely poor or inadequate patent law surrounding new areas of interest. Currently with genomics, we are experiencing exactly the same thing. People are patenting things which in my opinion shouldn't be patented because of obviousness or lack of known function. It is a sad state of affairs what's going on in the patent office, and it has been going on for a long time. So, because there is such an ill-defined situation, a lot of these issues are being worked out in court. I could go on, but I won't.

Hughes: Genentech created a clinical partnership for tPA in 1983.

Heyneker: I was on my way out when that happened. I think that I participated financially in that partnership. It was a very successful partnership.

More on the Early Days of Genentech

Patenting and Publishing

Hughes: Do you remember that Bob Swanson wanted to hold up publication on tPA? Does that ring bells with you?

Heyneker: Very vague.

Hughes: How often did it happen that Swanson or one of the other nonscientists said, "Don't publish that work quite yet"?

Heyneker: I think quite often, and rightly so. We were at a company, and there was much more at stake at the company than the early publications. I don't think that we had a problem with it. The general policy was that we would first file for a patent, and then we would ask: is this the opportune time to publish? Most often, once you file for protection, that is an opportune time. The policy was not to keep things secret. The pros of publishing early by far outweighed the cons of not publishing. We got extremely good people on board because of that policy. We were in high esteem with the academic world because of our publication policy. People knew what we were doing.

Hughes: As we discussed, although Swanson had a background in chemistry, he did not function at Genentech as a scientist. He functioned as a CEO. Presumably he came to this issue from the standpoint of what information should Genentech let out and what information should be kept secret.

Heyneker: Well, I think that we should give Herb Boyer some credit here. Herb Boyer is cofounder of Genentech and an extremely good scientist. He championed the policy of publishing quickly.

Hughes: Always?

Heyneker: Absolutely, from the beginning. So, Herb had a lot to say in this area policywise. He made an extremely good decision here. Also, Tom Kiley as [Genentech legal] counsel had a lot to do with publication policy. He was in a good position to determine if it was in Genentech's best interest to publish.

Assessing Boyer's Early Role

Hughes: Do you think that in the beginning Swanson made most of the decisions that related directly to the corporate aspects of Genentech, and policy on what I look upon as academic behavior was left to Boyer? There wouldn't be an argument there?

Heyneker: Maybe, probably sometimes. I was not close enough to understand exactly the subtleties there. Boyer was in general hands off. One of his policies was to let the scientists at Genentech shine. He did not want to play the role that he was the chief scientific officer dictating what was going on. He was very much in the position to let us—the young postdocs, the young scientists—make our own decisions and help shape the company. It was incredibly forward thinking of him. He created a very positive environment that way.

Hughes: I've talked with Herb, and I agree with what you are saying. But playing devil's advocate, you could also say that it was expedient for Herb to not be closely associated with Genentech at a time when he was being criticized for having founded Genentech and berated for its relationship with his own lab at UCSF. Also, it was an exciting period of research in his UCSF lab so why should he claim research at Genentech?

Heyneker: [pause] I don't buy it. I really think that Genentech was Herb's baby. I think that it was the best thing that he ever did, and he knows it.

Hughes: The best thing even above the development of recombinant DNA?

Heyneker: Well, yes, I think so.

Hughes: Why do you say that?

Heyneker: Well, I'll give you my opinion. First of all, recombinant DNA was not all his own doing. He was part of a select group of people who step by step got there. He did some relevant experiments with Stanley N. Cohen which gave him this very strong patent. But I think that his real claim to fame, together with Swanson, was that you could commercialize this technology. I should give Swanson just as much credit. But perhaps Swanson came more from an uninformed point of view. He said, "Look, this technology is so new, so great. Can we do something with it?" He asked that question of Boyer, and Boyer had to think

about it and said, "Yes." As a scientist, knowing what the technology was capable of doing, or at that time was not capable of doing, and extrapolating into the future, I give Herb a lot of credit.

Hughes: Herb had thought of the commercial applications before ever meeting Bob.

Heyneker: I bet you.

Role of Art Riggs

Heyneker: Here I have to bring Art Riggs into the picture. Herb was approached by Art Riggs very early on, to do certain things. I think that Herb's insight was influenced by Art Riggs as well. Art Riggs was very much a visionary. Herb Boyer also was a visionary. Probably that's why those two got on. Herb was always in for things that were unproven. He had an incredibly good knack to see how far these things could go. But so had Art Riggs. He really brought in the synthetic DNA capabilities.

Art Riggs wrote a NIH grant application on the expression of somatostatin in bacteria. When he couldn't get that grant, he used the same sort of reasoning to go to Herb Boyer to get it done. When Boyer started Genentech with Swanson, they needed a project; Riggs was aware of the situation, and presented the somatostatin project to them. Swanson wanted to start with insulin, but Riggs convinced them to start with somatostatin. In retrospect, this was the right choice—Riggs was darn good. So Boyer surrounded himself with the right people from that point of view. You know why? He was a very gregarious, very positive, enthusiastic guy, with a very good vision.

Hughes: What year was Riggs in Boyer's lab?

Heyneker: On two occasions he came to Boyer's lab to do a sabbatical.

Hughes: Do you remember any conversations about commercial applications?

Heyneker: Yes. I think that Art Riggs's strength was more in the entrepreneurial aspects and the conceptual aspects than in carrying it out. He was extremely good in grasping the possibilities.

Hughes: Why didn't he found a company? Or join a company? Or do something that was directly commercial?

Heyneker: He is very academic. He was not interested in that. His role as a collaborator suited him very well. He could continue to do the things that he was interested in. At the end of the day, I think that it was extremely smart what he did.

Hughes: Why?

Heyneker: The fact is that he did <u>not</u> join Genentech, but ended up with yearly royalties.

Hughes: From the Riggs-Itakura patent.

Heyneker: Yes. It gave him so much independence and a stream of financial tools. What he liked about that was that he could do the things he wanted to do. He never changed his lifestyle. He has always been an extraordinarily modest guy. But this financial independence gave him the opportunity to pursue whatever he wanted to pursue in science—glorious, wonderful!

Hughes: It took a while for the Riggs-Itakura patent to issue—1987 was it?

Heyneker: Was it that late? I don't know.

Hughes: Riggs didn't know that the patent was going to be so lucrative.

Heyneker: I don't think that he ever started from that financial point of view. He started from a scientific point of view.

Hughes: What I understand you to be telling me is that the patent royalties gave Riggs the money to do what he wanted to do in science. But he didn't know that until later when he began to receive royalties. So what was his reason for not joining Genentech?

Heyneker: He liked what he was doing. He liked City of Hope. He was dedicated; he was committed; he was loyal. I don't think it was in his vocabulary. I wouldn't be surprised if Genentech tried to hire him. I think that he was one of the most creative guys.

Herman de Boor and the Improvement of Expression Systems

Heyneker: I'd like to talk about some work that was being done by Herman de Boor, a very creative guy we hired very early at Genentech. He put a lot of time and effort into improving the expression system and understanding the factors influencing expression of heterologous genes in bacteria. Remember, we were struggling with production of interferons in bacteria, and we got very poor results initially. So, Herman de Boor was investigating and trying to understand why. One of the things that I think was particularly exciting was his idea of making hybrid promoters by combining aspects of one promoter system with aspects of another promoter system. He built this so-called tac promoter, which is a combination of the tryp promoter with the lac promoter. He achieved the control of the lac promoter and the strength of the tryp promoter, but also he learned an enormous amount about how promoters really worked. So I felt that he was very creative, unique, a great resource for Genentech to further our understanding of gene expression.

Hughes: What years was he there?

Heyneker: I hired him, as a matter of fact, around 1979, and I think he stayed until 1985.

Hughes: Was he in the molecular biology department?

Heyneker: Yes. He was first in my lab, and then he went to Dave Goeddel's lab. He had his sort of independent lab—a small group.

Hughes: Where were the hybrid promoters used?

Heyneker: At the end of the day, I don't think that they were used, but indirectly the knowledge was used. Hybrid promoters were one aspect of his work. He also came up with a very creative way to look at codons—the utility of bacterial codons versus eukaryotic codons and the preference of one type of codon over the other. I think that our basic knowledge really was increased dramatically.

Authority Over Scientific Direction

Hughes: That scientists made decisions about science was okay with the business executives?

Heyneker: That's a good question. At least in this arena we told the business people how it was. We had a lot of authority there, and we held on to it.

Hughes: What kind of arguments would you make to Swanson or whomever?

Heyneker: Well, the simple argument was that this whole company was based on science, and that what we accomplished was the result of creative science, so I think that it was a pretty compelling evidence. I think that Genentech, in general, understood the value of their scientists—of their personnel.

Hughes: There's that famous saying attributed to Swanson that Genentech's most important asset walked out in tennis shoes every evening.

Heyneker: Yes, in sneakers.

Hughes: On the other hand, Swanson was a businessman, and the way you have a successful business is to sell products—a very simple-minded statement of mine. Nonetheless, it might take some negotiating by the scientists to make it clear to Swanson and others that the company needed more than going after insulin or whatever.

Heyneker: Yes, but I think that there is nothing wrong with having to justify your existence.

Hughes: No, but you could convince him?

Heyneker: Yes. I would have been very disillusioned if it was any other way.

Hughes: Well, you've named some instances where you weren't successful, like the vaccine program.

Heyneker: Right, fair enough, I see where you are coming from. I think that Bob Swanson had enough vision that it was a science-driven company. It was more like, what science to do and not. Once you decided what science is important, you had a lot of freedom. I think

that the business group had more to say in what areas we should conduct our science than anything else. That's where some clashes came about. For instance, they were not interested in vaccines, and I think that it was a mistake. Perhaps, it was not a mistake, but I thought that it was a mistake.

Genentech Culture

[Interview 9: May 29, 2002]##

Hughes: With Genentech, molecular biology begins to move in a serious way into industry. When you first started to work full time at Genentech, were you aware of a difference in the culture as compared to your days in in academic labs in the Netherlands and at UCSF?

Heyneker: What we tried to accomplish—and I think that we were pretty good at it, certainly in the beginning—was to maintain some sort of an academic culture but have the research more focused on commercial applications. We had no other guide to go by. The people joining Genentech, especially in the early days, all came from an academic background. So that was the culture that we were used to, and we continued that. At the same time, we realized that the people who stayed in academe looked at us with some caution or apprehension because they felt that we were no longer true academics, but that we sold our souls not perhaps to the devil but definitely to commerce. Apparently, for a lot of people that was a sin. I never subscribed to that. Most of the people that came to Genentech in the early days were excited that we could apply exciting molecular biology principles to something which hopefully in the end had some medical application and some commercial application. It was a win-win situation.

Hughes: Did any of your academic colleagues come to you in those early days and say something along the lines of, "Herb, you are making a big mistake?"

Heyneker: No, I can't recall that. It was more a silent treatment or whatever. I don't think people were vocal about it; they were apprehensive about it. What we accomplished at Genentech is unique. This initial skepticism gave way to—admiration perhaps is too strong of a word. Definitely people realized that we continued to do rigorous science and that we did publish the science—we didn't keep it secret—so that the research community at large could benefit from it.

Publication Policy

Hughes: Publication was a deliberate policy?

Heyneker: That was definitely a deliberate policy.

Hughes: Do you remember debate about that?

Heyneker: To have this policy yes or no?

Hughes: Yes, because it wasn't a given that in industry you would publish and that you would try to publish in academic journals.

Heyneker: Well, before recombinant DNA technology was established—I would use that as the molecular biology principle on which you can build a commercial enterprise—the divide between academe and industry was probably bigger, and the industry was basically the pharmaceutical industry. The pharmaceutical industry kept a lot of things confidential—not all. I think that there was always good research going on there as well, and I think that it was also published. I feel that a lot of the academics make too big of a deal out of it, but that is the backdrop.

What we consciously decided at Genentech was to have an open publishing policy—after seeing the patent lawyer so that the patent application could be written and filed. That was essential. But still the question always was, should we keep certain ideas, technologies, etc., trade secret or should we share? Herb Boyer deserves a lot of credit. He was very adamant that we should have an open policy, and I think that that was a very smart move.

Hughes: Another argument was that if Genentech hoped to continue to attract top scientists that the chance to publish was absolutely mandatory. Nobody would come unless they had that.

Heyneker: Well, not so absolute, but definitely it helped enormously, especially when people saw this sort of policy and were impressed by the quality of the papers. All of a sudden, of course, you attract a lot good people.

Intellectual Property

Patenting in Industry and Academia

Hughes: How did the opportunity for patenting transpire? Was it the wish to publish that often provoked the question of should this innovation be patented?

Heyneker: It's possible. I think that it is probably the other way around. I think for Genentech it was critically important to have intellectual property, to have protection around the things we were doing. As you know, it is incredibly expensive to develop a drug. If you go through all the pain to develop it and there is no protection so that the competition can compete with you for a fraction of the cost, that would be a very undesirable situation. Definitely from the beginning there was an understanding that Genentech needed patent protection.

Hughes: But it wasn't quite like patenting in the pharmaceutical industry in that the status of patents in biotechnology at the outset was not established.

Heyneker: Well, I'm not so sure. With the Boyer-Cohen patent, academia realized that it was important to protect this intellectual property, so it is not that academe was against patenting. There is a much longer history that if you make valuable inventions, they should be patented, and I think that that is a good policy. In the case of the Boyer-Cohen patent, it was an incredibly valuable patent and an enormous windfall for Stanford and UCSF. And rightly so. So I don't see this big divide that the biotechnology industry came up with this new set of rules what to patent and what not to patent.

Unsettled Issues in Early Biotech Patenting

Hughes: The *Chakrabarty* case was happening about the time that Genentech was working towards its IPO. Put simplistically, the question was, could living organisms, constructed by man, be patented, and it went all of the way to the Supreme Court. The investment world wondered if it was a safe bet to invest in this new technology. The science was a bit questionable, in their minds anyway.

Heyneker: Was it?

Hughes: I don't think that it was a given that the commercial application of recombinant DNA would be successful.

Heyneker: I'd like to dispute it a little bit. For instance, when Genentech went public, it was one of the most successful IPOs ever, which means that, yes, people might have had concerns, but they also saw enormous potential. If there is no risk, then there is no reward. It is a very good case that the public at large was betting on the upside, although there were, of course, concerns about patentablility and so on. So, the IPO is a good example that indeed, at the end of the day, the public was very much in favor of this new technology.

Genentech's Patenting Strategy

Hughes: Were people at Genentech worrying about whether a patent would indeed hold in this new field, or was it just a given?

Heyneker: Not really. There were a lot of issues which might, at the end of the day, determine if the patent was to issue or no. So what you do is lay down a portfolio of patents to build hurdles for the competition to overcome. You don't bet your future on one patent. You lay down a minefield of patents to really make it hard for the competition.

Hughes: Was that the strategy from the first?

Heyneker: I think that we were aggressive in patenting—not overly aggressive—but we realized that it was important to preserve value. Tom Kiley did a very good job. We were definitely already patenting from day one.

Hughes: It took a long time for the Riggs-Itakura patent, a very broad patent, to issue. I don't know exactly when that was filed, but I'm presuming it was around the time—

Heyneker: It was the patent on the somatostatin? The work was done in '76, right?

Hughes: Well, '76, '77, and I presume that it was filed right around that time. So, it was ten years before it issued.

Problems in Current Patenting Procedure

Heyneker: That's a whole different issue. As long as you can keep a patent application going—the clock starts ticking once the patent issues.

Hughes: But meanwhile, you don't have protection.

Heyneker: But once the patent issues, you have the protection. It means that the people who are infringing at that moment have to pay or have to stop.

Hughes: It is in a way an advantage to have a delay in the patent issuing?

Heyneker: Yes, but I am now on thin ice. For instance, the [Shmuel] Cabilly patent was issued, which work was done in my lab; Cabilly was a postdoc in my lab. The work was done in '82 or '83. This patent issued in 2002, and the clock started ticking then. Genentech gets seventeen years protection of work that was done twenty years ago. I think that it is absolutely ludicrous, but that is the way it is. It has nothing to do with fairness—it is a tactic. The longer you can delay it, the longer Genentech has protection.

Hughes: Who delayed it?

Heyneker: I don't know; there are politics and strategy involved. Patent strategy is very complicated, and there are lots of pros and cons to delay and to keep a patent application alive.

Hughes: When was the Cabilly patent application filed?

Heyneker: It must have been around 1982 or 1983, because it was based on the antibody work.

Hughes: But once a patent is filed, it is in the hands of the PTO. So, where are the politics?

Heyneker: As a rule of thumb, the patent office rejects all patents. Show me that your invention is truly novel and not obvious, et cetera. They've been timed by that. Is it the right way to approach things? I don't think so. But that is the way it works here. You get first a rejection, always.

Hughes: What is the advantage to the PTO?

Heyneker: Well, with this policy, they hope that half the patent applications will go away, because they are overworked, underpaid, understaffed. It is so important for U.S. policy to have a

smoothly operating patent office which really can deliver. They don't pay the people adequately; there's a huge turnover at the patent office; examiners most often have no clue what they are doing. It is a sad state of affairs for something which is that important for the nation.

Hughes: I thought that you were implying that Genentech was also playing politics here?

Heyneker: Possibly, if you can delay issuance by having a continuation in part or by bringing new evidence— It is not my field, but there are a lot of ways you can keep a patent going. If there is an interference, you have to overcome the interference. That takes years and years. There's no hurry on either side. The result can be that indeed a patent issues twenty years after the fact.

Hughes: What about that interval when there is no patent, and yet the work has been published?

Heyneker: Once the patent issues and you are infringing it, you have to deal with the consequences.

Hughes: So it is retrospective.

Heyneker: Of course. To put things in perspective, the Cabilly-1 patent issued some time ago, which means that there was some framework around cloning and expression of antibodies. People were aware that this [Cabilly-2] was coming, so you keep the patent alive by divisionals and continuations in part. The Cabilly-2 patent is a much more rigorous patent; it is much harder for companies to go around it. I think that this Cabilly-2 patent has been challenged and has been in court for a long time, which means that it has endured the court actions. So a company which is infringing will think twice to challenge this patent again in court, because it has been challenged, and it has overcome the challenges. So, all of a sudden, Genentech is sitting on a very valuable patent because the world is using antibodies in many new drug applications.

Hughes: Is it so broad that virtually any company—

Heyneker: Well, if you want to express antibodies in a heterologous system—so not in a natural environment but in bacteria or fungi or eukaryotic cells—you have to knock on Genentech's door.

Hughes: All right, let's see what else we have here now that we are discussing intellectual property. Do you remember that Genentech participated in *Chakrabarty* as a friend of the court? Kiley wrote an *amicus curiae* brief in that case.

Heyneker: I sort of recall that, but I don't know much about it.

Genentech's Status in Intellectual Property Protection

Hughes: I'm trying to establish how much knowledge there was among the scientists about the things that were happening external to Genentech and yet impinged upon Genentech. Or

were you scientists just nose to the grindstone, letting the business types and the attorneys worry about things like that?

Heyneker: Well, true. I think that Tom Kiley is not somebody that likes to keep his nose to the grindstone.

Hughes: What do you mean by that?

Heyneker: He's flamboyant. He definitely likes to participate in the broader picture concerning patenting. I think it was right. It was great for Genentech. Those early involvements on that level must have helped Genentech enormously. I think that it was fantastic. That was definitely the way to go.

Hughes: Kiley was a high-profile patent attorney at a relatively young age?

Heyneker: He rose to the occasion. I think that he absolutely enjoyed that, and that is good. You have to establish yourself and build a name for yourself, and that's the way he did it.

Further Criticism of Patenting Procedure

Hughes: Did Genentech as a result of Kiley's endeavors—and others who came after him—become known as a company not to mess with in terms of intellectual property? Of course, people did mess with it, but was Genentech known to be a formidable adversary in the courts?

Heyneker: Unfortunately, formidable has a lot to do with how much money you can spare for that. If you are a small company without the deep pockets required, you can try to be formidable, but the guy that has the most money normally wins. There is hardly any justice. Justice, I have come to understand, is just for ignorant, innocent people. It is not about justice; it is about money. So, when Lilly was cross with Genentech and basically tried to declare all of Genentech's patents invalid, they were making good progress. The case was tried in Indianapolis, Indiana, of course where lobbying was going on. So the court was hardly neutral, and I think that Lilly was on the way to victory. One of the real positive fall-outs of Genentech being acquired by Roche was that all of a sudden Genentech had extraordinarily deep pockets, and Roche was not to be messed with. Therefore the case was settled in no time, and at great expense to Lilly. I'm convinced that if Genentech did not have that extra resource, the outcome could have been completely different. No justice—money. I was very unhappy about it.

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Hughes: You arrived at Genentech in 1978, and you left in 1984. In those six years, was there a noticeable shift in patenting strategy or the way Genentech was handling its intellectual property?

Heyneker: A shift?

Hughes: Yes. The field by then had blossomed. The industry was beginning to grow. Is there a maturation of patent law in respect to biotechnology that might have shaped the way Genentech went about protecting intellectual property?

Heyneker: I can't recall that there was a sudden shift.

Hughes: What about a gradual?

Heyneker: Yes, probably. I am convinced that Genentech learned the ropes along the way. We got more and more patent attorneys on board. We became definitely more a business unit, for sure.

Hughes: What did you have to go through when you wanted to give a scientific presentation?

Heyneker: Well, it needed to be cleared by the people who protected Genentech's intellectual property.

Hughes: You would submit a draft of the talk in advance?

Heyneker: Yes, or a summary, or it was verbal. I never found that it was very onerous. It was more like, make sure that you are not jeopardizing the strategy of the patent department.

Hughes: Do you remember instances where you had to change or omit remarks?

Heyneker: No, I can't really recall. I was in agreement with the review policy. I felt very strongly that Genentech needed to protect its intellectual property. I never had a serious conflict with it.

Hughes: But that would be very different than giving a paper in an academic setting—

Heyneker: I'm not sure. If Boyer and Cohen had talked about their ideas before they had patented them, it would have cost academe a couple of hundred million dollars.

Hughes: You mean before they filed for a patent?

Heyneker: Exactly. I think that it is common sense. I don't see a big difference between academe and industry—even then. In Holland, where I came from, they were a little bit further behind the eight ball. It was more up to the inventor if he wanted to patent. At UC and Stanford, I get the impression that even then professors were encouraged to see the patent office if they felt that they made an invention—which is great. I think it is exactly the right thing to do. But to say that this patent strategy is something different between academe and industry, at the end of the day I don't think so.

Hughes: There was criticism—

Heyneker: So what? There are a lot of whiners. Often they are short-sighted people who don't want to patent anything. They don't understand what it takes. They get their money from public funds. They owe it to the public or to the government or to wherever they get their money from, to try to capitalize on that investment as well as they can.

Hughes: I've heard that argument. What about the argument that by encouraging practical application, you downplay basic science? You deter young people from taking up basic science questions because there is no patenting opportunity and hence no money.

Heyneker: Well, I think that didn't happen. There are a lot of brilliant young scientists cropping up. I don't think that it has diminished our understanding of biology. I think if anything it has increased it. To focus on stuff which has practical applicability means more work on humans instead of on Chinese hamsters. We are more to the point where there are a lot of basic questions to be answered where potential applicability might be a little bit more obvious. I don't subscribe that you need to study all sorts of esoteric biological systems in order to further science and understanding. There is more than enough freedom to pursue it. The work on the worm, *C. elegans*, has progressed fantastically. Work on *Drosophila*, the fruit fly, has progressed fantastically. A lot of model systems—the Zebra fish—have been sequenced in their totality.

Basic Biological Research

Heyneker: I gave you just a few examples of studying model systems where you can really focus on the biology and the understanding is going on. Perhaps people have to justify it a little bit more. There's nothing wrong with that; it's very expensive. I feel that if you want to put money aside for research, you would like to see a return on it. Everybody would—academe, industry, it doesn't matter. You have an obligation. Like a scientist has to do good science. If he doesn't feel like it, if he feels that his heart is not there, then he should not be in science.

Hughes: Well, some people might argue, what do you mean by "return"?

Heyneker: Understanding.

Hughes: Oh, not just coming up with an invention that can be applied?

Heyneker: No, true understanding of how things work.

Hughes: Hasn't it been found with the evolution of genetic engineering that even if one has strictly commercial ends one cannot, in most cases, produce a sellable product without knowing the biology?

Heyneker: Correct. I totally agree with you. I am very excited about our understanding of human pathology and our knowledge of immunology. We know so much more, to a large extent thanks to the new era of molecular biology. I think that we have started to address significant issues of human suffering: autoimmune diseases, arthritis, cancer, viral infections. I am amazed how much progress we have made over the last twenty-five years. There will hopefully be some more great drugs around to treat significant diseases, and I think that our knowledge base has increased dramatically. How quickly we understood AIDS and the virus, an incredibly complicated biology. Not that we have a solution yet, but at least we know in exquisite detail what is going on, and I think that is marvelous.

Hughes: Not enough to make a vaccine yet.

Heyneker: Case in point. If we could easily mount an antiviral response to it, AIDS would have been eliminated a long time ago. It is attack and counterattack. But the fact that we now know how the virus evades immune surveillance gives us a better insight how these things evolve. That is extremely basic science, and it might have some practical applications. Here is a good example of how basic research and applied research work hand in hand.

Value of Patents vs. Publications

Hughes: You yourself are an inventor on twenty-one patents.

Heyneker: More. I think it is over thirty.

Hughes: I'm quoting from your CV.

Heyneker: Cabilly-2 just issued.

Hughes: It used to be that one way of evaluating a scientist was by the number of his or her publications, not patents. Is that changing? Where does number of patents possessed stand in the evaluation of a scientist?

Heyneker: Publication is probably the more gating item. For instance, I think that there are ten patents with me and Goeddel, and some other people perhaps, on the human growth hormone. And there is one seminal paper on human growth hormone, namely its expression.

Hughes: So the paper has more value than the patents?

Heyneker: I think so. At the same time, what is changing is that a lot of research is carried out in groups, so a piece of research is described by a whole bunch of scientists and therefore it becomes less clear who really made the most significant contribution. So if you want to evaluate a person based on publications, it is not always that easy. Number of publications is also very deceiving. Watson and Crick's paper in *Nature,* which was I think one page in total, in my opinion was a little bit more valuable than a lot of reviews on a mediocre subject. Yes, you want to know if a scientist does publishable work. I like to look where he published it, and also I want to use it in an evaluation to talk to him about it and see what contribution he really made in that research.

Hughes: If you were thinking of hiring a scientist, where would his list of patents figure in?

Heyneker: If I would hire for an industrial position, I think that it would look very good. I would say, my goodness, he is doing things with practical applications.

Marketing Licenses

Hughes: Were you involved in any way in the licensing—not the licensing process per se, because I assume that was handled by the legal department—but in passing the necessary information for the use of this license to the licensee? Do the scientists enter into that process at all?

Heyneker: Maybe in the later stage, once the license has been issued and the licensee wants to learn a little more about some particulars about the technology. That's when I imagine the scientist would come in. No, I can't recall that I have been actively involved in the licensing process.

Hughes: One of the criticisms of university patenting offices, including UC's, was that they didn't do much about pushing the licenses.

Heyneker: So what? That is the prerogative of the company.

Hughes: Well, it costs a lot to patent, and the criticism was that university funds were being wasted on obtaining patents that then sat on the shelf.

Heyneker: I think that 90 percent of patents are not worth patenting. Perhaps we need to be a little bit more critical in pursuing patents. A lot of the patents are not really critical and valuable. They are too detailed, too narrow—you can easily get around them. It is always very valuable to determine, "Is this truly patentable?" And, "Should I patent it, or should I keep it as a trade secret? Should I publish it?" Publishing might also be a very good deterrent, because once you have it published, nobody else can patent it. Yes, you can waste an enormous amount of money by pursuing patents which nobody is really interested in licensing. Of course, they end up on the shelf. But the more critical ones which people would love to license, the company has the option to give the license or to say that this is my territory and I am going to keep it for myself exclusively. They do the calculation and choose the one that is more advantageous.

Hughes: Was one of the responsibilities of Kiley and the other attorneys at Genentech to see that the patents were licensed, which would bring in, I assume, a sizable income?

Heyneker: I don't know what the policy was at Genentech. You should talk to Dennis Kleid.

Hughes: I did,[8] but I don't remember asking him that question.

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8. See the oral history in this series with Dennis Kleid.

Restrictions on Former Employees

Hughes: When you or anybody leaves Genentech, what kind of restrictions are put on transmitting the knowledge that you are carrying around in your head?

Heyneker: In California, you can put very few restrictions on that.

Hughes: Why do you limit it to California?

Heyneker: The laws of California say that you cannot be prevented from using what you know in your head.

Hughes: How would you, anyway?

Heyneker: You can't. One of the major risks that you run if you have a disgruntled employee who wants to leave, some of your trade secrets might become exposed. But in general, when you leave on good terms, there is a mutual understanding how you move forward. I think that it is very difficult to put very strict rules and regulations around it. You can make a contract for the first year—you should not engage in similar activities—but even that is difficult to enforce in California.

Hughes: I imagine that most scientists have their own slight variations on how they do experimental procedures. When they leave, the variations and improvements leave with them.

Heyneker: The way you go about doing your experimentation is very difficult to put restrictions on—impossible. I don't think that it applies to me directly, but it is something to be concerned about in a company if you get a lot of disgruntled employees. You run the chance that some of your valuable assets will be out of your control. So I think it is a very good policy—

Hughes: —to keep people happy.

Heyneker: If you have a happy environment, people will love to work there, and only then do you get the good output.

More on Genentech Culture

Hughes: Well, Genentech makes a big thing of its culture.

Heyneker: Still?

Hughes: Certainly retrospectively.

Heyneker: When you have four thousand people, it is a little more difficult to keep that culture. We had a very unique culture, I have to say.

Hughes: Do you think that the stories reflect how it really was?

Heyneker: I don't know what you are referring to.

Hughes: Well, in the early days Kleid and Goeddel working around the clock, taking breaks to put Nerf balls through hoops. The practical jokes—

Heyneker: Those were not the stories.

Hughes: Those were not the stories?

Heyneker: I think the culture was that you worked hard and that you played hard.

Hughes: Well, worked hard—and played when you were waiting for an experiment to mature, is the way I heard it.

Heyneker: Waiting for yourself to mature, is another way to put it.

Hughes: Were you the only one who had children in those very early days? Maybe Tom Kiley did, but he didn't become an employee at Genentech until 1980.

Heyneker: Dennis might have had children. I think I was not the exception to the rule.

Hughes: Well, the way Goeddel and Kleid like to tell it is, they worked very long hours.

Heyneker: Goeddel was definitely there always long hours. Goeddel is like a bulldog with a bone: you can't pry it out of his mouth. I think it is his strength; he will pursue it until the end, until he succeeds.

Hughes: And what was Dennis doing?

Heyneker: I think he was working hard as well. Perhaps not with the same sort of intensity.

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Heyneker: Goeddel is a different personality than Kleid and I am. I would not be very good to be as driven as Goeddel. But I compensated for that by trying different things or shifting my line of research in a slightly different direction. I don't think you even do that consciously; you find your niche. My niche was different than Dave's and Dennis Kleid's. Dennis and I were probably a little bit closer from the perspective of that philosophy. I think that it is good; I am glad that we were different. I see it over and over again.

I just came from a brainstorming session with a company I consult for. Just by sitting in a room with different people and freely thinking about it, you increase your number of ideas drastically—especially if people come from slightly different disciplines, different approaches. A lot of the really positive things about Genentech, especially in the early days, are that there was a lot of camaraderie, very little competition. If there was competition, it was friendly competition. We knew that Goeddel was trying to get the interferons, and we were not trying to sneak behind his back to get the interferons first.

We were more than happy and super excited for him to succeed. The reason was that we all had in mind the success of Genentech because we had all a part in Genentech. That is a big difference with academe, because often in academe the competition is who is there first, and there is no encompassing company which was one step above to serve the common denominator. The sad thing is that competition is often stimulated because people have to survive on grants. It is an inevitable problem in academe.

The Changing Relationship of Biotechnology and the Pharmaceutical Industry

Hughes: Were early Genentech scientists aware that you were setting certain precedents for how this new science would be done in industry?

Heyneker: Yes, we were aware of that.

Hughes: In what ways were you aware?

Heyneker: Before Genentech, there was academe and there were the pharmaceutical companies, and they were basically two extremes. We were wiggling in between, with huge repercussions. Now, twenty-five years later, biotech is an absolutely essential part of the pharmaceutical industry. The way research is being done in the pharmaceutical industry is by collaborating with biotech. So biotech is now an integral part of drug discovery. When we started, we were an uneasy experiment, and Eli Lilly, out of necessity, collaborated with us. Unfortunately, that turned into a love-hate relationship. I think that I touched on how impressed I was with their ability to bring insulin to the market, and how saddened I was by their policy to push Genentech out of the way. But Lilly was the first to embrace this biotech company, to help it.

Currently it is absolutely the rule. It is a very efficient way to do science, especially risky research. For a big pharma, to work with a biotech company specializing in a certain area gives them access to a new technology. If it doesn't work, they say goodbye, and they don't have to deal with laying off people and all of that sort of stuff. So, for them it is an effective way to look at new technologies, new areas. For biotech, without sponsorship from big pharma, we would not have survived as long as we did. So it was an absolutely synergistic relationship, and Genentech can be proud that it pioneered that.

Hughes: There was Kabi, too.

Heyneker: Of, course. Now there are about 1,500 biotech companies in the United States, and I tell you, one way or another, they need this interaction with big pharma. I think it is a very interesting development. Big pharma focuses more and more on other aspects of the drug business, namely the approval process, the development process, marketing and sales, dealing with the FDA—huge challenges. I don't want to say that pharma is giving up on in-house research, but a good portion is being done by biotech.

Hughes: Is it a factor that most molecular biologists prefer to work in a biotech company which is a hybrid with the academic world that they came from—

Heyneker: A halfway house.

Hughes: —rather than in a pharmaceutical company which has all of the trappings of corporate life?

Heyneker: I think that you are right, although there were a lot of successful people in big pharma as well. Let's not paint a black and white picture, because there are a lot of good things about big pharma, and I think that biotech is always the wonderful environment.

Hughes: We are talking in terrible generalities, which don't apply to specific cases.

Genentech's Board of Directors

Hughes: Switching to the board of directors, how aware were you that there was such a thing? As you probably know, it was in the early days three people—Boyer, Swanson, and Tom Perkins.

Heyneker: Well, by assimilation over time, I understood how corporate structure is organized in the United States and probably in the rest of the world. Yes, I was very much aware, of course, that Swanson, Boyer, and Perkins were in charge.

Hughes: How was that awareness transmitted?

Heyneker: Well, I was a postdoc in Herb Boyer's lab. Bob Swanson was checking with me every week, seeing if we made a breakthrough in the expression of somatostatin. And Perkins gave the money. So it was pretty simple.

Hughes: Was Perkins around a lot?

Heyneker: No.

Hughes: Would he wander through the labs the way Swanson did? Never?

Heyneker: Never, I don't want to say. Perhaps he came once or twice with Swanson, probably when a breakthrough did happen. He was more involved with corporate strategy, patent strategy, that sort of stuff.

Hughes: When did other people come on the board—Dave Packard and people connected with various companies partnering with Genentech?

Heyneker: Who is the guy from Fluor?

Hughes: Don Murphin.

Heyneker: He was one of the earlier guys, and he stayed on for a long time.

Hughes: What did he do for Genentech?

Heyneker: I don't know. Well, I think the guy was okay, but there was a huge disconnect; I was in science and he was in corporate finance at a big construction company. Fluor invested early on.

Hughes: They did, and they chose Genentech to develop their fermentation technology.

Heyneker: Yes, I think they made a very astute investment there. They must have made out like bandits. Good for them. They definitely bet on a very promising horse.

Hughes: There was no scientific advisory board in the beginning. What was that about?

Heyneker: Nobody could do it better than we could. [Hughes laughs] Why are you laughing?

Hughes: At the ego. Well, other companies didn't do it that way. Look at Biogen. They paraded their Nobel Prize winners around the universe.

Heyneker: Where did that get them?

Hughes: Touché. [laughter] I am guessing that their board was an investment strategy. It was a way of showing the venture capitalists and investment bankers that Biogen had some pretty hot stuff. How could you have a Nobel Prize winner or a prominent scientist on your scientific advisory board if you weren't pretty good? And yet Genentech didn't use that strategy.

Heyneker: No, I think we had our work cut out. We were picking the low-hanging fruits. We knew that after insulin and growth hormone, we were very interested in the interferons. There was a list of protein therapeutics which we were going after.

Hughes: Right, but presumably Biogen had a similar list.

Heyneker: Case in point. It doesn't matter if you have an astute scientific advisory board; you have to work it out. I don't think that you would move any faster by being smarter. We knew what we had to do. I maintain the fact that we had broad synthetic DNA capability kept us ahead of the game for a while, and we were basically the first in most of these endeavors, including interferon. I know that Walter Fiers, who was one of the guys in Biogen, worked very hard on interferon, and we beat him to the punch. It must have been a difficult time for them.

Hughes: I suspect that because there was a lot of prestige in the founding group of Biogen—and not surprisingly a lot of ego—they didn't have teamwork. They did a lot of Biogen's early work in individual labs, and there ended up being some competition, even amongst themselves. They didn't seem to have the cohesive approach that Genentech did.

Heyneker: It was very European-based. A lot of the people came from Europe.

I think that you said it right: Genentech was a more coherent company. And Genentech hired a bunch of guys who knew a thing or two about cloning, so we worked very fast. We probably had a longer history than most other people, and we cranked it up.

Effort to Recruit Donald Fredrickson

Hughes: An effort was made to recruit Donald Fredrickson for vice president of research.

Heyneker: That position was clearly meant to have a prestigious guy. It was a political move.

Hughes: He was director of the NIH at the time of the recombinant DNA controversy. So, a lot of federal policy regarding recombinant DNA was being shaped, at least indirectly, by him. The Recombinant DNA Advisory Committee reported to Fredrickson.

Heyneker: So, it was definitely a political coup if we could have had him.

Hughes: Apparently, you didn't want him.

Heyneker: Who me, personally?

Hughes: No, you scientists collectively. I don't know about you. What about you?

Heyneker: I can't recall.

Hughes: I heard that the scientists in the trenches at Genentech didn't want a person such as Fredrickson. They wanted somebody at the height of his scientific capability, not a symbolic—

Heyneker: Figurehead, fatherhead. I think that was true. To a certain extent, Herb Boyer was that figurehead, and he understood it so well, and he gave the scientists in the trenches—to use your words—the opportunity to shine. I think Boyer, to a certain extent, played that role, and we didn't need another one.

Genentech's Business Strategies

A Mixture

Hughes: A little bit on business stages: I've seen Genentech described as going through three different phases.[9] The first was contract research and development—I don't think that I agree with this assessment—then the licensing—but that is really going on at the same time—and then in-house manufacturing and marketing.

Heyneker: I don't agree with that either. I think it was much more concomitant as a way to raise money and knowing that we could not develop every product ourselves. We had a strategy to license and partner with other companies on certain products, but at the same

9. Peter Daly, *The Biotechnology Industry: A Strategic Analysis*, London: Frances Pinter, 1985, p. 74.

time, we kept products for ourselves, for instance human growth hormone, which was one of the first products that we cloned and expressed. [It] remained with us to a large extent. Perhaps I should take that back. Kabi was a partner there. Didn't Genentech sell it themselves in the United States?

Hughes: Yes, they did.

Heyneker: So, it was a strategy where, yes, we used partnerships to pay for the development work, but from early on, we tried to retain as many rights as we could to get into the manufacturing and sales business. To say phase one, phase two, phase three—no. It was a mixture.

Swanson's FIPCO Vision

Hughes: Today, I was looking back over the earliest Genentech documents, and in one of them, and I think it was 1977, Swanson expressed a goal of turning Genentech into a FIPCO, a Fully Integrated Pharmaceutical Company.

Heyneker: He said that. His goal was always to become fully integrated.

Hughes: Why did he have that idea? Where did he get it from?

Heyneker: It was his belief. He felt that if you want to really become successful and make money and play in the big league, that's exactly what you have to do. That's why we installed that big fermenter at Genentech early on, although it would never run.

Hughes: I noticed in his presentation to investor groups that he used Genentech fermentation capabilities as one of the company strengths.

Heyneker: Swanson, from day one, realized that the opportunity was to build a fully integrated pharmaceutical company. He followed his business plan extremely well. Apparently, after several years of operation, the plan was still on target.

Hughes: Do you think that Perkins wasn't so much a part of the business strategy, that he was more involved with getting further investment?

Heyneker: He was not a person who would come out to rally the troops. I think that he is a very reserved man, so he would focus on strategy—bigger issues. He would not bother to come down to the trenches. What happened in his discussions with Swanson, and what part he took in strategic issues, I don't know.

Hughes: Do you think that Swanson was using specific companies as models? What I'm trying to get at is, how original was his vision of Genentech? Or, was he taking pieces from—

Heyneker: From where?

Hughes: —his business school training, from companies that he admired, from talking with Perkins? How much of this strategy was the creation of Robert Swanson?

Heyneker: Well, there must have been quite a bit of creation by Robert Swanson because there were not that many examples he could learn from.

Hughes: Well, he could take bits and pieces from various sources.

Heyneker: And I hope he did. He got his training at the Sloan School [of Management] at MIT. That it is a very good business school, a very practical school. I bet he learned his lessons there quite well. But still I think that he went into uncharted territory. So, lots of credit to him how he carried it out and how he managed to get money from Kleiner Perkins, which was a fantastic group.

Widening and Narrowing Corporate Focus

Hughes: I imagine that I see a broadening of the vision in the late seventies. In the beginning, you've said that you were targeting human proteins for use in therapy. You were a drug development company, right?

Heyneker: Yes.

Hughes: By the late 1970s the fields are spreading out.

Heyneker: To?

Hughes: Swanson is talking about applying recombinant DNA technology to food processing, industrial enzymes, agriculture—

Heyneker: Was that the late seventies or was it the early eighties?

Hughes: He started talking about it in the late seventies.

Heyneker: Sure, recombinant DNA technology, of course, had application everywhere.

Hughes: Application at Genentech was what he was talking about. He was advertising Genentech as a company that was going to, or already had, moved into various fields, including vaccines.

Heyneker: There was also a lot of competition. Don't forget that Cetus—we have not talked about them yet—had started. You probably know that Swanson, very early on, did talk to Cetus, to interest them in his plan. He wanted to incubate that plan at Cetus, which went nowhere. They thought it was too early to apply recombinant DNA to make commercial products. But once Swanson was getting successful and focused on the pharmaceutical industry, it was Cetus who preached to the world that we were going to make the millions. But Cetus was going to make billions, because they were focusing on big industry, the industrial area.

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Heyneker: Not succeeding in their mission or making a dent in the industrial area, they changed their plan back to the pharmaceutical area, just at the time that Genentech launched Genencor and really was attacking the industrial area. And we were very successful in doing that. What I want to say is that it is often a matter of timing. When is the time right to do something different?

Hughes: Genencor was spun off—it wasn't an in-house deal.

Heyneker: But it was a recognition by Swanson that there was value there in the industrial area.

Hughes: Swanson had the vision early on that there were all of these possible applications of recombinant DNA in a variety of fields, and Genentech in one way or another was going to apply them. He was not talking about spinning off companies. But then very quickly he narrowed his vision back to Genentech being a drug company.

Heyneker: Well, I think he realized how expensive it is to develop drugs, that you cannot continue to broaden your scope.

Hughes: But that could have been an excuse to decide Genentech was not going to develop drugs; it was going to do industrial enzymes.

Heyneker: I'm glad he didn't do that. [laughter]

Hughes: I guess that is a stupid thing for me to say because by then Genentech had cloned somatostatin, insulin, growth hormone, et cetera.

Heyneker: I think we were firmly on our path to the pharmaceutical industry. He definitely had the vision—we all had the vision—that recombinant DNA was a novel way to make all sorts of products, that you could branch out in other areas. That we were discussing that and that that was crossing Swanson's mind is very logical, especially since Cetus was teasing him by saying, "Look guys, the industrial area is where the excitement is." Of course, you are listening to that and of course, you are being influenced by that, but I think that Genentech kept to its knitting and did it right.

Epogen: A Genentech Miscalculation

Heyneker: The only thing we did wrong was that we did not focus on the true winners. From that point of view, Amgen, at the end of the day, became the winner.

Hughes: Epogen?

Heyneker: Yes. They happened to embark on a product that turned out to be a multibillion-dollar project, and we did not see it. It was in our vision; we were aware of Epo, but we never thought that it would be such a big market, and that's very unfortunate.

Hughes: Well, how many research directions could you have gone in those early days?

Heyneker: Well, that would have fit in exactly with our strategy. It was definitely low-hanging fruit.

Hughes: Do you remember discussions?

Heyneker: Absolutely; we didn't believe that it was a big product. We did work on it to a certain extent to see if we could clone it, but it was not an effort that we felt was key. We really focused on tPA, and we missed the boat on Epo.

Hughes: But that is with hindsight. Probably, at that time, tPA looked like much more of a winner than Epo.

Heyneker: Yes. It is definitely hindsight, but at the end of the day it is the value of your product that determines your growth. So, Amgen could grow way beyond Genentech, basically because it had a successful product.

Hughes: Do you think that Amgen really knew what it had, or was there some surprise in that?

Heyneker: I bet you there was some surprise in that. I think they executed extremely well.

Hughes: Is that due to George Rathmann and his strategy?

Heyneker: Yes, and Gordon Binder was very good. They were very astute. Genentech had the opportunity to buy Amgen. They looked into that and they decided not to. That was probably a major mistake.

Hughes: Life would have been different. [laughs]

Heyneker: I feel a little co-responsibility for this, with a lot of other people, because Epo was clearly a product that we could develop, and it was a product that you obtain by cloning—end of story. And we were good at it. In those days we at Genentech were cloning all the genes, all the low-hanging fruit, and we missed this one.

Hughes: But, in defense of you scientists, you knew that you could do it in the lab—

Heyneker: So we should have done it.

Hughes: But wasn't the next step to do some market analysis?

Heyneker: Right, I understand and I agree to a certain extent with you. Research is cheap. Development, manufacturing, becomes expensive, and that is when you place your bets. By cloning it first at least you have the intellectual property around it; you have serious bargaining chips. I think that we should have been more alert that this was something that we should have done.

Hughes: Was there anyone in the nonscientific areas of Genentech who should have been in on decisions like this in terms of what the product potential was?

Heyneker: Yes, we should have been more diligent and had a stronger sense of what other products we could have identified and cloned. I realize that twenty-twenty hindsight is always easy. But at the same time, I have always felt that here was this fledgling company called Amgen cloning this Epo, and we should have done it. End of story.

Hughes: Do you remember it being a low point when you heard that Amgen had cloned Epo?

Heyneker: The low point came much later when their market capitalization became much bigger than Genentech's.

Hughes: And still is?

Heyneker: Yes, I want to be associated with the premier biotech company, and we were. I am very competitive from that point of view. We were so close I perhaps should have—we collectively should have caught this one.

Hughes: It wasn't easy to get.

Heyneker: The more reason why we should have gotten it. We had more experience than anybody else.

Building Corporate Value

Hughes: Swanson repeatedly tried to instill in all Genentech employees the idea of building value in the company, rather than merely making profits. That is Dennis Kleid's view anyway. I guess building value would mean a long-term perspective rather than getting the killer product of the moment.

Heyneker: That sounds all very beautiful.

Hughes: But you don't believe any of it?

Heyneker: No. Let me be more positive. Yes, of course building Genencor off Genentech, like its culture and enthusiastic workforce, were all essential ingredients for long-term success of the company. But there is no better remedy for success than having a killer product where you make a lot of money. Let's call a spade a spade. I know Swanson well enough that he was not shy of making a lot of money. So, yes, to do it ethically, building an exciting company where people would love to come so that you can attract the best people—all the advantages—yes. At the same time, I think for any company it is imperative to make money. Perhaps that comes right back to Epo—the more reason that we should have caught that as a product.

Genentech's Initial Public Offering

Hughes: We've skirted around the IPO. How big a deal did Swanson make it at the time? Were you in on the buildup and some of the setbacks?

Heyneker: Of the IPO or of the troubled market in general?

Hughes: Well, both, but I was thinking particularly of the IPO, which was delayed somewhat. I'm trying to get a feeling for how much information was transmitted to you scientists, not only about the IPO but in general about the administration of the company.

Heyneker: I think we scientists were kept pretty much in the dark. We were not actively involved in getting us to an IPO.

Hughes: Do you think that was appropriate?

Heyneker: Yes, in those days, sure. I had no clue what it took to get an IPO. I was totally ignorant of the stock market and all of that stuff. I bet you the Fred Middletons, the Tom Kileys, and the Swansons were very involved. It was an incredibly important moment in the history of Genentech because it meant that we could raise a lot of money to fill our coffers and have enough money to execute our plan. We scientists were not that involved. I just remember what a fantastic success it was—what a glorifying success.

Hughes: You remember that day specifically?

Heyneker: Of course. I was incredibly proud to be a part of a company which had such an incredibly successful IPO.

Hughes: Did anyone have an inkling how successful Genentech was going to be?

Heyneker: No, I don't think so. There were a lot of people who said, "You could have raised much more money. If you priced your securities higher, you would have raised at least twice as much money." Bob Swanson, I recall, always said that you have to leave some money on the table to make it successful for investors. There's nothing better than that the investors feel that they made a good investment. He was so right on that, because not that much later Cetus went public. They were much more greedy. They raised twice or almost three times more money than Genentech did. They never got over their offering price ever again. At Genentech the stock went to eighty and then came down under the offering price for a few weeks, but then things went well, and the stocks split and split and split. People who invested in Genentech made out like bandits, while people who invested in Cetus—the stock went under the offering price and never returned to the offering price, and it made it very hard for Cetus to raise money again. Genentech was the darling of Wall Street, and Cetus was a problem child. So I think Bob Swanson was absolutely right to leave this sort of money on the table. It must have helped Genentech enormously later. Everybody wanted to help Genentech. It was a very astute strategy.

Hughes: Were realizing at that juncture that maybe you were going to be quite a well-to-do man because of your association with this company?

Heyneker: Well, Sally, that depends on the definition of well-to-do.

Hughes: Well, better off than being an academic scientist?

Heyneker: I dispute that. The strategy of Art Riggs and Keiichi Itakura was much better. I think that they made much more dollar return than we scientists at Genentech.

Hughes: Because they negotiated more money?

Heyneker: No, well, part of the deal was royalties. I think there are a lot of other ways to create wealth. Look at Peter Seeburg and other people who got an academic patent. When that patent was licensed from U.C., they shared in the patent, and they got a significant return on that, I would say more than most people at Genentech. So it is not that academe will not benefit from this patenting activity.

Hughes: I didn't mean to paint it black and white. Nonetheless, stock options are a fact of corporate life and presumably some incentive.

Heyneker: A huge incentive. That's why we were so committed to making Genentech a success. I think it is a very smart way to do it. There are one or two reasons why academic people would like to go to companies like Genentech, instead of going to big pharma where they get a good salary, but they get very little return on their inventions. I think that it is a great way to create a win-win situation. To participate in the upside by being creative is a very democratic way to do things. This is the right type of capitalism.

Hughes: Did it make a difference that Genentech after the IPO was obviously a public company and consequently publicly accountable, at least to the stockholders?

Heyneker: Probably it did, but the culture didn't change that drastically. I think that we were made aware that there were responsibilities associated with public status.

Hughes: Such as?

Heyneker: Conduct.

Hughes: Conduct?

Heyneker: Well, you have a responsibility to your shareholders. You are visible, so you can't afford to be rookies anymore. That's probably one way to say it. Did we understand it exactly at that time is another question. Well, it becomes serious when a company is publicly held. I think that you have to be careful for lawsuits and that sort of stuff. Also, you are in a different position. You have to account on a quarter-by-quarter basis for your actions, so that you have the luxury to carry out your plan according to a longer-term view. But again, I don't think that it changed the culture at Genentech very much. We still had a lot of hard work and fun, and we had a significant amount of money in the bank to really do things right. All in all, I think that the IPO was a very positive thing.

Hughes: I heard that there was a hiring committee, I think for scientists, established very early on. Do you remember?

Heyneker: Yes, I think so. It rings a bell.

Hughes: Do you remember the circumstances?

Heyneker: No, refresh my memory, and I might.

Hughes: They way I heard it was, as Genentech began to grow, there was some concern about the quality of scientists that were being hired in divisions other than molecular biology. The committee provided a means for vetting scientists before they were hired.

Heyneker: I can't recall it in that detail.

Monoclonal Antibodies

The CEA Antibody Project

[Interview 10: June 4, 2002]##

Hughes: Today we are talking about monoclonal antibodies.

Heyneker: This is a project that is near and dear to my heart. The cloning and expression of the heavy chain and light chain of a particular antibody was carried out in my lab and was analyzed by Ron Wetzel's group.

A little bit of history: It was Art Riggs who proposed the expression of a particular antibody, an antibody against carcinoembryonic antigen, CEA. He wanted to clone the gene coding for this particular antibody, expressed in *E. coli*, with the hope to make large quantities of that particular antibody, but also to give you the opportunity to manipulate the antibody. For instance, if you are interested in not expressing the entire antibody but only a fraction thereof, it can be done quite easily because the tools to manipulate the DNA are there. So, you could be very interested in Fv fragments [variable fragments] or Fab fragments [fragments antigen binding] or mutagenized variable region of this antibody to influence the properties of the antibody, for instance, to influence the binding strength of the antibody—affinity. So, the technique opens the door to very interesting next-generation antibodies.

Hughes: The concept was Art Riggs's?

Heyneker: Yes. Art Riggs, as I have mentioned several times, has played a very significant role in finding interesting things to do for Genentech. It started, of course, with somatostatin, which was a prelude to insulin, and then the antibodies were a very exciting thing to do. I was really very excited to be able to do that in my lab. I felt that it was a great opportunity.

Hughes: The early eighties were a period when many companies were interested in monoclonals, either for diagnostic purposes or, down the line, for therapeutic. Did Riggs have that idea independently, or was he caught up in the mania about antibodies at that time?

Heyneker: A very good question. I think the antibody mania was a little bit later than when he came up with this idea. There, of course, was interest in antibodies; there always has been interest in antibodies ever since the concept of monoclonal antibodies was invented by Cesar Milstein and—who was the other?

Hughes: Georges Kohler.

Heyneker: But I don't think that there was yet a frenzy to use antibodies for therapeutic purposes. It was coming, and I have to say that Art Riggs didn't act alone. There was quite a bit of work on this CEA antibody. It was done at City of Hope, and I think Jack Shively deserves to be mentioned here. It was known that this antibody was quite specific for colorectal cancer.

Hughes: So there was a potential application?

Heyneker: There was a potential application—exactly. And again, Art Riggs was willing to stick his neck out and do things that other people hadn't done. It is not just expression of a polypeptide chain, as we did with all of the proteins mentioned before, but two proteins had to come together. An antibody is basically two heavy chains and two light chains, and they have to find each other and reconstitute into an antibody. Of course, mammalian cells do that, especially specialized mammalian cells like plasma cells. Their task is to produce and secrete antibodies. We tried to mimic this process in bacteria. So, it was a real challenge to make something biologically active here. The cloning per se was only one part of it.

Genentech's Method for Producing Monoclonals

Hughes: I thought prior to this time, the major way of producing monoclonals was through hybridoma technology.

Heyneker: Correct, this was potentially a completely novel way to make antibodies, and since it produced one particular antibody, you can call it a monoclonal antibody. The reason that people call them monoclonals is that when you isolate antibodies from serum or when you immunize with a particular antigen, you get antibodies against different epitopes on the antigen you present. Polyclonals are antibodies derived by immunization, to differentiate them from antibodies derived by hybridoma technology or in our case by cloning and expression in a heterologous host.

Hughes: Was anybody else cloning antibodies at that time?

Heyneker: Well, we were aware of another group.

Hughes: Celltech.

Heyneker: Yes. I know that we beat them to the punch, and very recently the court has agreed with Genentech that we were the first. This is a very recent announcement. It is the Cabilly patent that is quite well known. I'm getting ahead of myself. Yes, there was competition, and Celltech in England was trying to do similar things.

Hughes: What was the original part of Riggs's concept, or did Celltech have the same idea?

Heyneker: I think the concept was not completely off the wall, because the idea that you can express heterologous genes was by then reasonably well established. The novelty was one step further: that you need to express two different genes and then the peptides have to come together.

Shmuel Cabilly

Hughes: Well, talk about that because apparently it was fairly complicated science, and Cabilly comes into the story—he must if he is on the patent.

Heyneker: Yes, of course he comes into the story. He was a postdoc in Art Riggs's lab, and he spent time in my lab to learn the tricks for cloning.

Hughes: He didn't know them before?

Heyneker: He didn't know them. He learned a lot, but at the end of the day it was not really he who had cloned it: It was my faithful technician Bill Holmes who did the cloning. But listen, Cabilly was very much involved. He played a significant role. He was first author on the paper, and therefore he and others like Bill Holmes, Ron Wetzel, Gene Perry, and myself were on the patent. [interruption to check names of patent inventors] Gene Perry is not on the patent, and obviously Art Riggs is on the patent.

Patenting and Inventorship

Hughes: What are the determinants of inventor order on a patent?

Heyneker: I think what is a more important question is what determines if you are an inventor. The order on a patent is not as important or as political as the order on a paper. So quite often what people do—and I think that is the case in this situation—is put the authors on the patent in alphabetical order. That's quite common.

Hughes: So, you can't really tell much about contribution as you often can by the author order on a publication.

Heyneker: Correct. Patents are hardly ever used as a publication. It is often mentioned separately that you have some patents, but they are not as important as publications.

Hughes: Will you comment on the choice of the inventors? I surmise that there were many papers written on this topic and that there were probably more authors than became inventors.

Heyneker: That is quite often the case. You have to make a contribution, and the person who writes the patent is responsible to verify that you really made a patentable contribution. So, often people who just do the work—let's say a technician that you tell, "Hey, today I want you to do this that and the other thing" and who can do very good work—rarely will such a person be on the patent. But if there's a lot of independent thinking and organization how to carry out the experiment and how to make the chances of success greatest, that is, of course, a different order of participation.

Hughes: Holmes would fall under that category? He was much more than just a pair of hands?

Heyneker: Cabilly and Holmes demonstrated that the clone was the correct clone; they sequenced it; they showed unambiguously that this was the CEA antibody.

Monoclonals and Genentech's Research Priorities

Hughes: As you know, it is a very broad patent. Does it then follow that the invention—the science itself—had many applications, and how aware were you at the time?

Heyneker: This is a good question, Sally. Here is the situation: When we did the work around 1982-'83, I always believed that it was very important and exciting, and so did Ron Wetzel and Art Riggs and probably others. But I do recall that I had to beg our patent department at Genentech to patent this work, because this was not in the mainstream at that point in time for Genentech. As a matter of fact, Genentech did not aggressively pursue the opportunities opened up by this work in the beginning.

Hughes: Because it was a recombinant DNA company?

Heyneker: Well, this was a recombinant DNA product, don't get me wrong.

Hughes: That's true.

Heyneker: But they had their hands full with tPA. Genentech could not develop a lot of other things simultaneously. I understand that you need to focus.

Hughes: When people talk about the low-hanging fruit and the list of products that might be produced by recombinant technology, you don't hear about antibodies.

Heyneker: If you are talking just about antibodies, you can make lots of antibodies of a particular kind using hybridoma technology. That's exactly what you are doing with recombinant DNA technology. Where the excitement comes in is, once you have the genes for heavy chain and light chain, then you can manipulate them. You can make, as I have mentioned, Fab, Fv, single-chain antibodies—lots of things you can't do if you use the gene the way it is organized and arranged in the eukaryotic cell.

Hughes: It shouldn't have taken much imagination for Genentech management to see that this way of mixing and matching antibodies could get around problems that others were finding in producing therapeutic antibodies, mainly the problem of using a mouse antibody in a human being.

Heyneker: Yes, you can definitely circumvent that problem.

Hughes: Why wouldn't Genentech management have seen that this new way of manipulating antibodies had a chance of circumventing that major problem?

Heyneker: Well, I can give several answers here, but I think that the fair answer is that Genentech absolutely had to focus. To do research is very cheap compared to doing development on a product. All of a sudden, you raise the bar a few notches because it takes a lot of money and dedication to bring a product to the marketplace. So you place your bets, and then you have to focus on that. If you do too many things at the same time, which all cost some money, you don't get there; it needs a very concerted effort to get there. At the same time, I do believe that Genentech should have supported on a lower level further research on recombinant antibody—no question about it. I was very disappointed that it didn't.

Hughes: Did you argue for doing something with antibodies?

Heyneker: Absolutely. I think that it was probably the main reason why I left Genentech.

Hughes: What about your disappointment about the demise of the vaccine program?

Heyneker: Well, the vaccine program was much farther removed from my bench, from my lab.

Hughes: Had that already happened by the time antibodies were scuttled?

Heyneker: Yes, and I was not pleased by that either, and I pleaded relentlessly with Jim Gower and others that it was a big mistake. You have to look at these issues not just from a scientific point of a view, but also from a business and financial point of view.

Hughes: It is an interesting fallout from the hype over tPA, which I guess now is doing fine, but there were certainly some doubts in the late eighties—

Heyneker: Well, I think it's a very disappointing product from a marketing and sales point of view. It is not a billion-dollar drug—which we absolutely hoped for—and it cost Genentech great, great problems.

Prioritization of Research Projects

Hughes: How are decisions made in terms of projects that will or will not be pursued?

Heyneker: Well, they were probably made by the management team and the board—so in the conventional way.

Hughes: What kind of information feeds into those decisions? A Tom Perkins isn't going to know much about tPA. The information has to come from somewhere—not from the scientists doing the work?

Heyneker: Not from the scientists doing the work. It will come from the vice presidents of research, and there were a few of those—David Botstein and David Martin [and others]. There definitely was a representation of the scientists on the management team. But the overriding constraint was that Genentech needed to get a next product to the market successfully.

Hughes: Growth hormone wasn't approved yet?

Heyneker: No, it was not approved yet.

Hughes: As I remember, it got through the FDA in 1985. There was a lot of worry about that.

Heyneker: Of course.

Hughes: By 1983 there were something like fifty companies trying to make antibody-based products, many of them focused on diagnostics. The first therapeutic didn't get approved until—

Heyneker: '92 or something like that.

Hughes: Late. So, was the board thinking, not only do we have to focus on tPA and growth hormone, but all these companies are trying to make a buck on antibodies and they aren't getting anywhere. Why should we get into this field?

Heyneker: Well, first of all, I cannot answer that question because I did not participate in those board decisions or in those management decisions, so I only can talk to you about my frustration.

Hughes: But weren't you talking to Dave Martin?

Heyneker: Yes, and I think that Dave Martin was probably defending my position. But there are many more pieces, which are often conflicting, and you have to make a decision. I was not at those board meetings, but I almost guarantee you it was focus, focus, focus, and I am not against that. It is enough of a challenge to get a product through the FDA, and, yes, we firmly believed that tPA would have been the absolute wonder drug, although I was very surprised that it was so much smaller than we had anticipated.

Hughes: So, you also thought that tPA was going to be tremendous product?

Heyneker: Yes, but did I have access to all sorts of marketing data? No. But there were people at Genentech who were much better at that—at least supposed to be much better at it.

Hughes: And there was a competitor.

Heyneker: Yes, streptokinase is a much cheaper product. We didn't think it was as good. Urokinase was also following.

Hughes: What about Eminase, which was the SmithKline product?

Heyneker: TPA based?

Hughes: I don't know.

Heyneker: Of course there was competition, but at the same time, I think that Genentech had a very strong patent position. We were the first to clone all of these genes, which does not always automatically translate that you get what you deserve. We discussed that before.

Hughes: We did—the injustice of the justice system.

Heyneker: Absolutely. But if there is competition, either perceived or real, there is even more of a reason to focus and be as fast as possible to the marketplace. So, look, I appreciate it but I still feel as of today that Genentech should have spent a million dollars a year to pursue the research opportunities for antibodies and move that field at a much faster pace. They are currently extremely interested in antibodies, and this Cabilly patent, which has finally issued nineteen years after the fact, is of course an enormous windfall for Genentech.

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Heyneker: Ron Wetzel did just a fantastic job reconstituting the light chain and the heavy chain and showing that indeed you could make an antibody that is specific against CEA and thereby proving that we had the right patent. Also he was very disappointed that we did not pursue this further, and he also left.

Hughes: Because of the decision against antibodies?

Heyneker: I can't speak for him, but I think so. We had so many opportunities. We were so excited about single-chain antibodies—Fab fragments—which nobody else could make. There was a whole slew of things that we could be doing. We could improve on the expression systems. I think that it was a treasure trove.

Hughes: One of the advantages of this technique was its ability to produce the light and the heavy chains independently. What did Wetzel have to do to reconstitute those chains? Did the previous work with the insulin A and B chains help?

Heyneker: Absolutely, I think Wetzel was A, an extremely good protein biochemist; and B, he had an enormous amount of expertise in refolding technology. So, that was our first approach. But later, as you may recall, in my lab you had a lot of work on secretion of product into the periplasmic space. That was the work that was done mainly by Greg Gray, and he came up with a very good system. It was the ST2 system, the signal sequence. We have mentioned it so I will not repeat it.

But anyway, we did secrete light chain and heavy chain into the periplasmic space of *E. coli*, and later we produced it in eukaryotic cells. In eukaryotic cells, the heavy chain and the light chain do come together, and we demonstrated that indeed those cell lines secrete antibody. But also once we were able to secrete into the periplasmic space, the refolding was done by the bacteria, and we could measure immunologically active product. So, all

in all, this whole technology had a lot of promise, and we did some of that work, and then it was shelved.

More on Genentech's Monoclonal Antibody Method and Intellectual Property

Hughes: In the beginning, you were producing the light and heavy chains in separate bacteria, and it was Cabilly's idea to produce both light and heavy chains in one cell? Why is that significant?

Heyneker: It was an important concept, because otherwise it means you have to keep two different plasmids in constant proportion to each other, and that in itself is not so easy to do.

Hughes: Why?

Heyneker: You will select for bacteria where one plasmid will survive over the other, by natural selection. For instance, when bacteria which only express light chain and heavy chain replicate, the ratio of one plasmid versus the other is changed. If some bacteria divide a little bit faster, then they will take over the culture. So, inevitably, you will segregate; you will get either one or the other plasmid.

Hughes: So how did you regulate the ratio?

Heyneker: Well, you can keep them both in sync if you put in different antibiotic resistance genes, one on one plasmid and the other on the other plasmid. I think we did that; I'm not sure. Who came up with that, I can't recall. If Cabilly—great. So often you brainstorm. You are in the lab, doing this work the whole day. You talk to each other the whole day. It might well be that Cabilly said, "Should we do this?" At the same time, is this a breakthrough? I don't know. Somebody would have thought of it, and I am very happy if it was Cabilly.

Hughes: It also could be the environment: You might have said something that provoked him to come up with the idea.

Heyneker: I think brainstorming is absolutely so valuable. That's why brainstorming we should always continue to do. The risk you run is that somebody might just say something; another person gets the gist or spark and says something which might be patentable. So who came up with the idea? You know, I think the group came up with the idea by participating and provoking novel thoughts.

Hughes: It seems to me that the patent system polarizes things because you've got to have inventors. In the publication system, you've got to have authors. Nowadays, you have many authors on a paper. You can't have as many inventors as authors, right?

Heyneker: You can.

Hughes: The preference of the legal system is to have fewer inventors.

Heyneker: It is not just the preference; it is much stronger than that. If you put people on a patent who have nothing to do with an invention, it can be used in court to knock down a patent. Also, if you don't put an inventor on a patent, and he can prove that he absolutely made a significant inventable contribution to it, it can also jeopardize your patent. So there is more to it than just choosing a subset of the people who might end up on a paper. Quite a bit of thought has to go into it. One of the tasks of an attorney who writes these patents for you is to determine who are the inventors.

Hughes: How do they go about that?

Heyneker: By interviewing the people.

Hughes: Thomas Waldmann wrote an article in *Science* in 1991 which caught my eye.[10] He said, "The ability to genetically engineer antibodies represents a quantum leap in immune intervention that is comparable to the immunological revolution initiated by the introduction of monoclonal antibodies."

Heyneker: Absolutely. I like him already. [Heyneker reads relevant section of article.] I think the guy is right on the money. I felt—and not just me; Ron Wetzel felt the same—that this [antibody technology] opened up just lots of opportunities.

Steps in Creating Humanized and Human Monoclonals

Hughes: Do you care to say anything about the development of successively human monoclonals, going from chimeric to humanized to human?

Heyneker: Well, sure. One of the things that we did very quickly was to exchange the mouse Fc region for the human Fc region. The Fc region plays a very important role in antibody immunology, B-cell immunology. There are lots of biological activity associated with this so-called constant region or Fc region. The antigenicity you elicit by putting a mouse antibody in a human is mainly against the Fc region that is quite antigenic. So if you can exchange that for a human Fc region, you don't interfere with the antibody per se because the specificity and the binding capacity reside in the Fab portion of the antibody. So, to make a chimeric antibody by replacing the human Fc region for the mouse Fc region was destined to work, and that's what we did.

Now, to go one step further and to humanize an antibody further becomes a little tricky, and that has to do with our understanding of the Fab portion of the molecule. People in 1983 understood that there were hypervariable regions interspersed with framework regions. So, the next thing to do was to exchange the mouse framework regions for the human framework regions because the hypervariable regions determine the antigen specificity and the binding specificity. So if you start messing with that or playing around with those sequences, you have a very good chance that you will change the binding

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10. Thomas Waldmann, "Monoclonal Antibodies in Diagnosis and Therapy," *Science* 1991, 252:1657-61, 1658 (June 21).

capacity. So, to humanize is really to try to make the antibody look human as much as you can without interfering with the hypervariable regions.

Now, to make a truly human antibody by building it up from recombinant DNA-derived antibodies, starting with a mouse antibody, is impossible because we don't know what type of hypervariable regions the human will put in. There is, of course, a lot of somatic mutation going on during B-cell development, and nobody knows what particular combinations of hypervariable regions the human—or mouse for that matter—will put in to get a particular binding affinity. It is unpredictable. To make a truly human antibody in a different species is technology which is currently being employed by companies like Mederex and Abgenex, where you start with a particular mouse where they have exchanged the immunoglobulin repertoire from mouse to human. That work was originally discovered and patented by Genpharm, which was a spinout of Genencor, and I will come to that when I discuss Genencor.

So, those are interesting questions, and we know much more about it now: the importance of chimeric antibodies versus normal antibodies. When we look back, the initial therapeutic monoclonal antibodies were not very promising. It was really a disaster, and it took quite a while before a next wave of antibodies came through the pipeline and became therapeutics. But now, after this false start, antibodies play a very important role in novel therapeutics.

The Issue of Research Focus

Hughes: I know it is after your time at Genentech, but do you have any insight into Genentech's revived interest in antibodies?

Heyneker: Sure, I have insight, but I was not directly involved at all. One of their most successful products currently is Herceptin which is a monoclonal antibody against a breast-cancer-specific antigen called HER-2/neu. This is a good example of immunotherapy.

Hughes: I understand that the origins of that work at Genentech were in Axel Ullrich's research on growth factors.

Heyneker: Ullrich was definitely at Genentech very much a visionary and an underappreciated visionary.

Hughes: Underappreciated by whom?

Heyneker: I would say by management. I would say that he was a little more futuristic. He was not looking at the low-hanging fruits. He wanted to understand a little better how the system works. He did a lot of work on receptors and interactions of growth factors or interferons with their cells. Receptors—EGF, IGF—those were lines of research he was pursuing.

Hughes: Well, I understand that he was tarred by the brush of basic science—that was one of the accusations.

Heyneker: Right. But you need these sorts of people to refresh your pipeline, to make sure that there is something novel to develop over time. I think it is very good investment, especially by a successful company which has a product on the market, to continue with an aggressive research program, and I think Genentech is doing it currently. I am not disputing that at all. I think that they understand that very well.

Hughes: Is there anything to be said about the low-hanging fruit versus basic science? One could say that the early companies went after what was easiest, or so they thought, but didn't put much emphasis on the biology.

Heyneker: I think that it is a little bit less black and white. First of all, I think Axel was not just an academic researcher. His goal was understanding how some of those hormones, the low-hanging fruit, truly worked, finding their receptor, their counterpart, how well they interfered in the biological system. So, that was not directly academic research. It was a logical and necessary step to really understand your product, what it was doing. But in general—and we touched on it before—basic research and applied research are no longer this great divide. That really changed rapidly. Genentech played a very important role to bring down this divide. Most people realize [now] that you can do very good basic research which has also at the same time applicability.

What Genentech was struggling with around 1984 was what to do with probably a limited amount of money. I probably didn't appreciate enough what it takes to keep all of these people at Genentech meaningfully employed and pay their salaries and develop a drug. I don't think that Genentech wanted to go back to the financial markets too often, because it was very diluted from stock, et cetera. So, I can understand that there was this need to focus.

Hughes: I know from talking to Swanson that Perkins was constantly saying focus, focus, focus, and Swanson probably paid a lot of attention to what Perkins was saying.

Heyneker: Well, he had to, right? I would say A, Tom Perkins was his mentor, and B, he was not a man to take lightly. I think that he could be very severe. He didn't say much, but you'd better pay attention. That is the sort of person he is.

Perkins came out of the high-tech industry. He was very much involved with companies like Tandem Computers. So what the high-tech industries went through were basically lessons learned which could be applied to the biotech industry. It was clear that in order to be successful in high tech, you also needed to focus on your product and not wander around and diddle in a lot of different possibilities. So, I think that Perkins was speaking from experience.

Hughes: Do you think that the model of the high-tech industry was a good one to apply to biotech, or were there cases when perhaps biotech was misled by applying principles that had worked for electronics? After all, biotech deals with living systems.

Heyneker: Absolutely, I hear you. I think, yes, you can easily misconstrue, and you cannot compare. What I really meant was the economic model rather than the technological model. I totally agree with you that when it comes down to science where you have to deal with living organisms versus silica, there are huge differences—timelines dealing with clinical trials—a completely different industry. But still I do appreciate, looking back with a

2002 perspective, that a reasonable focus is important, otherwise you don't get there. That still holds, and if we learned that from the electronics industry, so be it. But, at the same time, it is a balancing act. What people sometimes don't realize is that research is really quite cheap. So to keep things alive by sponsoring research without the commitment to develop it, for a successful company is probably a very smart thing to do.

V GENENCOR

Heyneker's Decision to Become Research Director

Hughes: Have you applied that principle in your later companies?

Heyneker: Well, perhaps by nature of the beast. At Genencor, I was research director; I was definitely sponsoring research activities. But Genencor needed to focus in order to succeed. So, I maintained it as a balancing act. But I still remember that I was very bitter that what I saw as a great opportunity and what Thomas Waldmann also saw as a great opportunity, we did not pursue. I was disappointed, perhaps a little bit disillusioned, that this tPA product was not what it was supposed to be.

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Heyneker: Somebody had it all wrong. Was the marketing research adequate, or were we believing our own altruistic viewpoints? Did we check it sufficiently? I really don't know. But it made me a little bitter, to be honest, especially since it was not the first time a mistake was made. The fact that we did not pursue the vaccine area that turned out to be quite lucrative I felt was also a flaw. So, I decided to pursue another opportunity when it was offered to me. That was to go to Genencor and be responsible for the research activities.

Hughes: How did the opportunity present itself?

Heyneker: Well, perhaps we should go back a little bit. Genencor, a joint venture between Genentech and Corning Glass Works, was formed in 1983. Gary Steele, who was the business development vice president at Genentech, was responsible for bringing those parties together. The goal of Genencor was to pursue industrial opportunities.

Hughes: Of recombinant DNA?

Heyneker: Of recombinant DNA technology—exactly. That was mainly industrial enzymes. I wanted to learn something new. I wanted to get more involved as a manager and be involved in decision making.

Hughes: Did this decision flow from your disappointments?

Heyneker: Could well be, because I felt that my ideas on applicability were not that far off, and I really like that aspect. So, when Bob Leach, the CEO of the joint venture of Genencor, approached me if I would be interested in that role, I took it seriously and decided to do it.

Hughes: Why did he approach you?

Heyneker: Well, he was probably looking for people at Genentech to get some expertise in recombinant DNA technology. He might have approached other people or somebody might have whispered in his ear that I might be an interesting candidate—I don't know. But I took it seriously and I decided to do it. The reason why I didn't think twice about it was that I never felt that I was leaving Genentech. I really felt that joining Genencor and helping make it a success would be indirectly a success to Genentech because they owned 50 percent of the company. So, I never felt that I left Genentech to go to either the competition or go to another company. Unfortunately, it turned out that other people at Genentech, and especially Bob Swanson, did see it that way. I was very saddened by it because I had hoped to stay much more in touch with Genentech, in an advisory role or whatever, and continue to be involved.

Hughes: You were going to a company that was 50 percent owned by Genentech and applying a technology in an area which Genentech was not.

Heyneker: Correct—not competing—exactly.

Hughes: So what was the problem?

Heyneker: I don't know. I think that the problem was more emotional, that I was the first scientist to jump ship.[1] That was probably the view of Bob Swanson.

Hughes: Do you think that he had any understanding of your disillusionments?

Heyneker: I don't know. I might not have told him that. Perhaps I did not understand myself as crisply as I did later what really bothered me.

Corning and Other Corporate Owners

Hughes: Why was Corning interested in forming this subsidiary—is that what you would call it?

Heyneker: Yes, or joint venture. I don't know exactly. I think that it was for financial reasons to a certain extent as well as for technical reasons. Genentech was the darling of Wall Street. People felt that it was a very interesting, exciting company. So to have the opportunity to see if you could repeat that in another area was appealing for a larger corporation. On top of that, Corning was developing interesting technologies based on their enormous

1. Roberto Crea left Genentech in 1982 to found Creative BioMolecules, Inc.

knowledge of glass and porcelain materials, which can be used as purification media. There are a lot of opportunities where, especially on an industrial scale, Corning had something to offer—especially from an engineering point of view. What I think appealed most to them was the opportunity to build another Genentech.

Hughes: Did they succeed?

Heyneker: I think Genencor succeeded in the end. It was a little bit of a rocky road, but by the time Genencor succeeded, Corning Glass Works was no longer a participant. They sold their stake to other corporate shareholders. Initially, it was sold to A.E. Staley, which was a sugar-refining company. Genentech also sold their stake after a few years, and Eastman Kodak, as well as a Finnish company, namely Cultor—not to be confused with Coulter Counters. Kodak became a major shareholder. Corning probably sold their interest in Genencor to Staley, but I think that they realized that it was not really their core business. It was a little bit of an odd situation. I got the impression that Corning wanted to focus on glass and especially on some high-tech opportunities like fiber optics, which became in later years a very successful business.

Hughes: What was Corning hoping to do with enzymes?

Heyneker: I think it was more a financial play. I don't think that they could use the enzymes themselves. The newer partners like Staley could definitely use the enzymes, because high fructose corn syrup, which is of course the product produced by the sugar refiners, is truly an enzymatic process to convert the corn starch into high fructose corn syrup. So, Staley was a company which had much more at stake or had a direct interest in the industrial enzyme business. So did Eastman Kodak, to a certain extent. They had a division, Eastman Chemicals, which was a big player in certain fine chemical markets, including certain celluloses—crystalline cellulose. So it was a much better fit with Kodak and also with Cultor. Cultor was in Europe sort of the equivalent of Staley, a big starch processor. So, those new parents were more directly involved and interested in Genencor.

Hughes: Do you think that a small part of Corning's original interest might have been to show that it was not only cognizant of but actually had acquired cutting-edge technology?

Heyneker: Absolutely. They did not want to be perceived as a stodgy glass company.

Heyneker's Views on Managerial Positions

Hughes: How did you yourself acclimatize to a very different field, both emotionally and in terms of the science? It was a radical shift—

Heyneker: From human therapeutics to industrial-scale enzymes?

Hughes: Yes.

Heyneker: It definitely was an adaptation process, but I enjoyed very much the challenge to be more in a decision-making position.

Hughes: That was what attracted you mainly?

Heyneker: I think so—well, also to have a bigger group report to me. I always like very much to talk science with the scientists—that comes naturally to me. I really enjoyed being with a group of scientists.

Hughes: I remember your saying many sessions ago that you didn't particularly like being vice president of research at Genentech. I'm not sure they called it that at the time. You were the first.

Heyneker: Right, that is true. I don't think that I was ready then. I really felt that I was not in a position to be in charge of my colleagues. I felt sort of artificial. I did not feel that I had much seniority over any of the other guys, so I did not want to create a situation that I had to call the shots.

Hughes: What aside from age made you feel differently about Genencor?

Heyneker: Well, age and experience.

Hughes: So, you felt that you were ready?

Heyneker: More ready. I think that you can say only in retrospect if you were ready. I think that I learned a lot at Genencor what it means to be in a managerial role.

Hughes: What did it mean?

Heyneker: Well, quite a bit of responsibility.

Hughes: Such as?

Heyneker: Well, the overall responsibility rests with you that that you stay on track with the things you are promising to your corporate partners—for instance, we had a big research contract with Procter and Gamble—that we really did deliver what we said we would do.

Hughes: How did you insure that happened?

Heyneker: Well, you can't insure that. You can only insure that you build a realistic program which has a reasonable chance of success. It is a balancing act. If you are conservative, your corporate partners might not like it. They might say, "I can do that myself." If you are too aggressive, and you can't deliver, you might have a partner who is very unhappy with you. So, I learned a lot from that. I also learned to really be in a more managerial position, although I must say that I had a great team of people around me. It was really delightful.

Colleagues

Hughes: Did you recruit some of them?

Heyneker: Some of them, yes. Some of them were in place; some of them came from Corning, like my boss, Bob Leach, and Stan Mainzer. There were definitely some people from Genentech that we recruited, like Dave Estell, a brilliant enzymologist/protein biochemist who really was instrumental in building the value at Genencor.

I also got an enormous amount of help from Wayne Pitcher, who was the vice president of development; he came from Corning as well. Research and development was split up, which turned out to be a good move because Wayne and I had a good interaction. He was much more senior than I was, so I used his knowledge to mold my research group, making sure that it was in line with his development group.

Genentech as a Model and a Culture

Hughes: To what extent was Genentech a model, or perhaps an anti-model, of what you wanted to achieve?

Heyneker: It was definitely a model.

Hughes: There may have been aspects, though, that you didn't want to duplicate.

Heyneker: I think that it is a very good question. Overall, Genentech was a fantastic model. I might have been, at one point in time, a little bit disillusioned. This might be a good time to say that overall, it was such a unique experience to be at Genentech, to see it grow, to see it become successful. I should be very thankful, and I am. The culture which we created at Genentech was very positive in general. We had an enormous amount of fun, while at the same time, we did very good science. It was a good combination of work hard, play hard. It is a good strategy to keep your people motivated. Science is not a nine-to-five job. You cannot force scientists to work long hours, come back at night, work on the weekends. They will only do it if they are charged up about the science, if they really like what they are doing. I think one way to make sure that people are dedicated is to create a very positive atmosphere.

So, we really tried to create [a culture at Genencor] which was related to what we did at Genentech. [It was] never the same, of course, especially since we brought in the Corning culture very early on. Quite a few people came from Corning, and they had just as much right to bring in their culture as we had the right to bring in our culture. At the end of the day, it was a very good marriage and very positive.

Hughes: Could you characterize the culture of Corning?

Heyneker: Well, Corning is a much more established, conservative, East Coast company, while we on the West Coast were in uncharted territory, building our own culture, being the first biotech company. The end result was that the Corning people loosened up, and the Genentech people realized that to build an industrial enzyme business is not easy. The reason why I say that is that in industry there are other parameters you have to deal with. Novelty is not enough. You have to deliver at a certain price and a certain cost. There is an enormous constraint on what your upside is. The low-hanging fruit for Genencor was

to find an enzyme which would clean your laundry a little bit better than what was happening before. So, it was measured in incremental improvements, rather than finding a novel therapeutic which was not there before. Those were real challenges. So we had to look carefully at cost structure, at value creation.

Hughes: And you could do that?

Heyneker: I couldn't do it by myself, but as a team we had to do it right. Wayne Pitcher was much more trained in the area of a true industry, instead of a fledgling biotech pharma.

Hughes: As you said, there was quite a difference in products, so what was the continuing attraction at Genencor?

Heyneker: Well, again, the attraction was that I learned a lot, that I helped shape the company because I had decision-making power—not that I am power hungry. It was good to look at research effort from a business point of view.

Jonathan MacQuitty

Heyneker: One person who really helped me there was Jonathan MacQuitty, who also came from Genentech. He came fresh out of business school from Stanford University, started at Genentech, and took the opportunity to become vice president of business development at Genencor around the same time I became vice president of research. I am a scientist with an appreciation for business, and Jonathan is a businessman with an appreciation for science. As a matter of fact, he came from England, where he gained his Ph.D. in organic chemistry, so he knows a thing or two about science. We became very close. It is a very useful combination to approach corporate partners if you have a team where the business understands the science and the science understands the business. So we were very complementary. Currently, I spend two days a week at Abingworth Ventures, and Jonathan MacQuitty is a partner at Abingworth Ventures.

Hughes: So, the relationship continues.

Heyneker: Absolutely. My initial interaction with Jonathan around 1984 became a true friendship, and we are working together on very similar issues. I will come back to this, because later in our Genencor careers, we had several spinoffs from Genencor where we found exciting technologies which were not really in the mainstream for Genencor, but there was value to be had. So we spun them out with the help of Genencor. Jon and I started companies under the umbrella of Genencor which both became quite successful.

Hughes: What were they?

Heyneker: Jonathan started Genpharm and I started GlycoGen.

Hughes: Were you doing any hands-on science at the time?

Heyneker: I had here and there a little project, but really I stopped doing hands-on science.

Hughes: How did you feel about that?

Heyneker: I had a hard time with that. I think perhaps I stopped a little bit too early, especially looking back. My real strength was in hands-on lab work. I was good at it.

Hughes: You had only had six years at Genentech.

Heyneker: That's correct, but I had two years at UCSF, and before that I had my research years in the Netherlands.

The Subtilysin Project and Procter & Gamble

[Interview 11: June 6, 2002]##

Hughes: Last time we talked about Genencor, mainly from the managerial and business side. Today would you talk about the science?

Heyneker: Sure. All of a sudden changing the nature of the work you are doing, going from pharmaceuticals to industrial enzymes, was a big step—also psychologically. I mean, we at Genentech were working on life-saving drugs, and all of a sudden, we were at Genencor working on enzymes that would help you clean your laundry. So, it was a different emphasis. On the other hand, it is important as well, and had its own set of challenges and also very interesting science surrounding it.

One of the subjects we were doing was to improve the properties of an enzyme, in this case for laundry applications. We used absolutely state-of-the-art high tech to accomplish that. The enzyme is serine protease isolated from a *Bacillus* species. It's called subtilysin. We determined its three-dimensional crystal structure. Then we deliberately made changes in this enzyme on the DNA level by mutagenizing the DNA and putting different amino acids in predetermined spots, asking by doing so would that change the property of the enzyme. And yes it did. We learned an enormous amount about the enzyme and its specificity and how we could improve certain properties. We became, I would say, really trendsetting in this area. Now, there is not that much competition in the industrial enzyme world, but I think we raised the bar a notch or two for the competition. We used high tech for low-tech applications.

Hughes: Were your competitors using recombinant DNA?

Heyneker: Yes, they were using recombinant DNA technology as well, although since we were quite early, we had an opportunity to file for patent applications. So Genencor had over time acquired quite a significant patent portfolio which of course helped them to establish themselves in the end as the number-two enzyme company. Now, we did not do that all just by doing good science. We also grew by acquisition of other companies.

The subtilysin program was probably the biggest program going on at Genencor. It was a program which was sponsored in its entirety by Procter and Gamble. We were very happy that we found such a big partner to help us get off the ground, because the barrier to entry

for an industrial enzyme company is huge. The competition will not sit idle. The competition, mainly Novo out of Denmark, had much larger resources than we had. So to find a way in and start occupying the same space was not easy. In retrospect, especially, it was definitely a tall order.

Hughes: Who was responsible for the relationship with Procter and Gamble?

Heyneker: Dave Estell was to a large extent responsible for that. He was the project leader, a very imaginative guy, really a good sales person at the same time, who could explain very complicated, technical things in an understandable way. Also, we made progress. The relationship with Procter and Gamble was not always the easiest, but that is to be expected. Overall, they had patience with us, and overall we delivered. If you currently wash your clothes in Tide, which is the premier brand for Procter and Gamble, you will find the Genencor enzymes in there. So, we built a very successful relationship with them.

Hughes: Was it a selling point that Genentech had this new technology of recombinant DNA? Was that why they came to you?

Heyneker: Absolutely. The rationale behind it was that recombinant DNA technology could be used in areas other than just the pharmaceutical area. The next area which came to mind was the industrial area, the area Cetus focused on from the beginning. Often with these sorts of endeavors, it is a matter of timing. I think that Genentech's timing in the pharmaceuticals was right. Then later branching out in other areas, making use of the knowledge you've acquired in the process, is a good strategy.

First Mover Advantages, the FDA, and Incremental Enzyme Improvements

Heyneker: As I mentioned, the barrier for entry in an industrial field is much more difficult than pioneering in a field where there is no competition in the beginning. Genentech was truly a pioneer. They were the first to make drugs using recombinant DNA technology. So, again you can call it the low-hanging fruit: There was no competition from different insulins; there was no competition from different growth hormones. Once you could produce it in bacteria, that was the obvious way to go.

Hughes: On the other hand, there were some kinks in the road that one wouldn't have encountered if one were producing industrial enzymes. I am thinking of things like clinical trials, FDA approval—all of that business.

Heyneker: Yes, that is a very good point. The FDA was very critical and cautious in the beginning because recombinant DNA technology was very novel, and a lot of people were very skeptical and very afraid of perceived dangers. So, I can imagine, indeed, that the FDA would be very cautious. However, I would say that Eli Lilly paved the way. The project they tackled in collaboration with Genentech, namely manufacturing, production, marketing, and sales of insulin, was a perfect example. The world knew that there would be a shortage of natural, that is, porcine-derived insulin. The FDA was very much aware that something had to be done to secure the supply of insulin, especially in a graying population.

Hughes: Just so I am sure of the point that you are making: Genencor was producing industrial enzymes by a new process, but the enzymes that resulted were marginally competitive with enzymes that were produced by other means?

Heyneker: That is exactly what I am trying to say. What the challenge at Genencor was, was not to make something novel but to make something already existing a little bit better. The enzymes which were being used in the laundry applications were produced by bacteria or by fungi, so the cost of these enzymes was not prohibitively high. The challenge at Genencor was to make a better product, or a cheaper product, or a combination of those things, but it was not that we were introducing an entirely novel product.

More on the Subtilysin Project: Research

Hughes: Give me an example of one product, and what you did to make it a more marketable product.

Heyneker: Well, subtilysin is a very good example. In the end, we were able to produce an enzyme mutant which worked better on a wider variety of stains. At the end of the day, it is the quality of the enzyme—therefore the quality of the overall detergent product—that counts. Customers come back because they are happy with the product. They believe that it is doing a good job.

Hughes: What did Procter and Gamble contribute in terms of the science?

Heyneker: I felt that it was a true collaboration. We had to come up with analytical technologies to show on a small scale that some of the mutant enzymes were indeed removing certain stains better. We had grass stains; we had blood stains—I tell you, this was a different world. At the same time, with many industrial products, if you do make them significantly better, a large existing product can be replaced in its entirety. So, the upside is significant. We took this very seriously, and so did Procter and Gamble. They helped us by doing larger-scale studies to see that it indeed was working. For example, farther into the development process, we had embarked on a mutant which looked quite good, and we scaled up a manufacturing process. There was all of a sudden a disaster because the enzyme which we delivered to Procter and Gamble on a large scale—this was being manufactured in huge fermenters—

Hughes: At Genencor?

Heyneker: At Genencor, yes. We acquired and built a stand-alone manufacturing plant where we could do fifty thousand gallons worth of fermentation. It was huge; I mean a really impressive scale. So, early on we delivered that enzyme, which was supposed to be the next best thing, but then all of a sudden, for one reason or another, the product separated out or precipitated and became an enormous mess. We needed to solve this, literally, in a few days. Procter and Gamble was of course extremely nervous and unhappy with us because the product did not work as advertised.

I remember that Scott Power, a very creative guy at Genencor, had to work day and night to come up with a solution. And he did come up with a solution. Often, when you are in a truly tight spot, that is the best time to be creative. That was a moment that could have made or broken our relationship with Procter and Gamble. It was very much like the insulin story where the first milligram of insulin was really a challenge. We had also here our set of problems, but mainly in the development/manufacturing area, and we learned an enormous amount from it. To manufacture these products on the scale I mentioned, in fifty-thousand-gallon fermenters, is a totally different world. You move your products out in big trucks, after purification; they are not something that you put in a vial. So it is definitely exciting.

Hughes: Where were the mutants coming from?

Heyneker: We had, of course, cloned the gene for subtilysin. Once we had the DNA, we used mutagenesis technologies—site-directed mutagenesis—to change the properties. We did also random mutagenesis because it was a little bit early in the day to rely solely on site-directed mutagenesis. The predictive power of making changes and correlating them with better performance was not there. We were building this correlation between mutants and performance.

Hughes: Does it tend to be in bacteria one gene, one enzyme? We are finding in higher organisms that genes work in synchrony, and that you can't knock out one or mutate one and depend on getting the effect you want. Is that what you were doing?

Heyneker: No, this is much more straightforward. We knew that we were after a particular enzyme, and it was not that this enzyme would influence a lot of other products. Luckily, that complication we didn't have, so we knew it was one enzyme, one product, one system to work on. We learned a lot from over-expression.

We needed to make this enzyme literally in ton quantities, which meant that every gram per liter more of this enzyme we could produce was a huge cost savings, and we needed to be at a certain level to be competitive with the existing enzymes. Our enzyme worked better, but, for instance, by adding twice the amount of the competitor's enzyme, you could accomplish the same goal. So, it was a matter of not only having a better enzyme, but also we needed to produce it very cost effectively. It was also a learning curve that we were on.

The Subtilysin Project: Development and Manufacturing

Hughes: Were you as the vice president of research leading the attack in all these different areas?

Heyneker: Well, no. A lot of these challenges were development and manufacturing challenges—how to scale it up, et cetera. Over-expression is not just to put the enzyme [gene] behind a stronger promoter. There are a lot of other tricks: how you grow your microorganism, what sort of nutrients you put into the media. So, there was a lot of conventional development going on.

Hughes: Was that existing knowledge?

Heyneker: No, we did not have much knowledge at all. There was some knowledge there, but I would say that we really had to build a lot of this from scratch. There were people in the development group who had some knowledge about this. They came out of the industrial enzyme world—they had spent some time at Miles [Laboratories]. But I think we learned a lot from doing it.

Hughes: So, the trucks that were going out of Genencor were delivering an enzyme that Procter and Gamble just had to put in their detergent?

Heyneker: Yes, that's right. Procter and Gamble demanded certain specifications, and we had to deliver according to those specifications.

Hughes: They didn't have to do any further development, once the enzyme got to Procter and Gamble?

Heyneker: Right, they didn't want to touch the enzyme, so that was our problem. We built this very efficient plant in Cedar Rapids, Iowa, for the manufacture of the enzyme because the Bay Area was way too expensive to build such a plant. Moreover, the bacteria which were pumping out the enzyme needed to be fed on a rich stream of nutrients, including sugars. So high fructose corn syrup and that sort of stuff were part of the diet of *subtilis* bacteria. We were better to find it in an area where those nutrients were very cheap.

Hughes: Because you were at the beginning of the chain of development, you probably did not have to spend much time in Cedar Rapids?

Heyneker: No, I didn't. That was where the manufacturing folks were. It is very educational for somebody focusing on the research part to understand what it takes to bring a product to the marketplace—what it takes development-wise and manufacturing-wise to really accomplish this. I really got a much greater appreciation for the challenges and the solutions those people found.

Hughes: Was there any difference in working with scientists at Genencor as opposed to those at Genentech?

Heyneker: No, not basic differences. I think that scientists are perhaps a special breed. You become a scientist because you like science, so I think that you find yourself surrounded by people who have similar interests, and it doesn't matter if it is in the industrial area or the pharmaceutical area. I must say that it's very interesting to be around those people. One of the real privileges to be in the science environment is that you meet a lot of people who are truly curious about technology.

Hughes: Research on industrial enzymes produced enough satisfying scientific issues to keep people happy?

Heyneker: Absolutely. I think so, because we truly took a state-of-the-art, high-tech approach to get there. We pioneered x-ray crystallography on an industrial enzyme to a certain extent, and it helped us to really understand this enzyme in excruciating detail. It really helped to get Genencor on the map. So, the high-tech approach was right. There were so many

challenges to overcome. A lot of people got really excited about it: "Let's solve this puzzle." We needed to put a lot of pieces of the puzzle in place to become successful. Looking back, the most satisfying aspect of working at Genencor was that it was a very significant challenge.

Genencor's Agreements with Genentech

Hughes: Genencor now makes products in health care.

Heyneker: They are starting to do that.

Hughes: You had no part in moving them in that direction?

Heyneker: Well, I always wanted to move them in that direction as soon as we could, but there was an understanding between Genentech and Genencor that Genencor would work on industrial aspects and would not touch the pharmaceutical area. I always felt that antibiotics were a field that would be open for Genencor, and I tried to push that early on because once we knew how to ferment, production of antibiotics, in my opinion, was also quite an interesting opportunity and very valuable. The penicillins and cephalosporins in the world were huge multibillion-dollar products, and still are. Genencor is looking at this in more detail now, because they are no longer bound by this charter that they could only work on industrial applications.

Hughes: When did the joint venture with Genentech come to an end?

Heyneker: Well, Genentech sold its stake quite early on, within a few years, but still the division was maintained—Genencor could not compete with Genentech.

Hughes: How could that be?

Heyneker: It was part of the negotiations, I assume.

Hughes: Even after Genentech sold its stake?

Heyneker: Yes. Well, don't forget: Genencor got licenses to all the technology developed at Genentech. I can understand that Genentech said, "Look, you get those licenses [only] in a certain field. We will not put a competitor in place." That was fair enough.

Filamentous Fungi

Heyneker: Before we leave this technical issue, I would like to mention some other products. One platform we developed at Genencor was the development of filamentous fungi as industrial microorganisms for the production of enzymes. We developed a lot of technology to accomplish that. It was really uncharted territory. Fungi are very

interesting, very important industrial microorganisms. For instance, penicillins and cephalosporins are all derived from a class of fungi which makes very important secondary metabolites. So, it was very useful to understand how we could transform those fungi and put foreign DNA into these microorganisms to give us the flexibility to make other products. We started from scratch.

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Heyneker: [Genencor] ended up with quite a rich patent portfolio in this area.

Rennin

Heyneker: One of the products we wanted to make was rennin. Rennin is used, as you probably know, in the cheese industry as a clotting agent to clot the milk and produce the cheese. Most rennin came from the stomachs of calves. It is a strange process.

Cheese making must be as old as the world is. Farmers, early on, experimented with all sorts of combinations and noticed that by combining these natural ingredients milk would clot and the result was quite tasty. So, that's probably how over time cheese manufacturing came into being. Calf rennin was expensive; the number of calves was declining—calf meat is not as popular anymore—and there were also some problems because the natural rennin process is not as well defined.

We felt that we could take over the market if we could produce rennin in a fungal background, and we succeeded. There was an enormous amount of opposition from the farmers and a lot of people maintaining that recombinant rennin was not the real thing and was not as good as authentic calf rennin. I think most cheese in the United States is currently produced with recombinant rennin. Even in Europe, I would say that the majority is produced now with recombinant rennin. It is much better controlled; nobody noticed a change in taste. It is all around a better product.

Hughes: Was the resistance due to the financial impact on the farmers who were producing calves?

Heyneker: Yes. The food industry is extremely conservative, and any change is resisted as unnatural. Still, as of today, recombinant foods have a very hard time getting accepted. So, yes, probably the biggest challenge was to overcome that stigma. We did not do it ourselves; we partnered with a major rennin producer in Europe, Christian Hanson. They saw the writing on the wall that with this new technology sooner or later recombinant rennin would be produced, and they wanted to be ready to participate in this field. They were quite aggressive: they understood the advantages of a recombinant rennin; and indeed they have done a great job in introducing this product.

Well, to wrap it up, Genencor also spent a lot of effort on enzymes involved in the conversion of corn starch into high fructose corn syrup, which uses a combination of three enzymes. So again, our knowledge of fungal microbiology and ability to manipulate different fungi came in very handy to produce these enzymes, like glucoamylase, on a very large scale. All in all, the challenge was probably greater than we had anticipated

when we started Genencor. We were probably naïve in building a company from scratch in the industrial area. But I think with the help of our corporate parents and by acquiring companies, we became quite a successful company. Currently, there are two enzyme companies in the world: there is Novo Nordisk and Genencor. All in all, it was a fantastic experience.

GenPharm

Heyneker: While I was there, Jonathan MacQuitty and I were always looking at new things, either for Genencor to do or what we could be doing. We stumbled on technologies which were outside Genencor's focus and charter, but they were quite interesting, and one of them became GenPharm. That was a technology identified by a scientist at Genencor, Herman de Boor, who came up with the idea to produce valuable proteins in the milk of cows. It is a very interesting idea because a healthy cow produces close to fifteen gallons of milk per day. If you can make valuable proteins in milk, it could be a very interesting proposition. But it was not something that Genencor could pursue at that time.

Genencor cloned and sequenced the lactoferrin gene and was the first to do so. That was their contribution to the startup company called GenPharm. Genencor had 10 or 20 percent of that company, and it started to lead its own life. Some other technologies were acquired, and I encouraged Jonathan MacQuitty to become CEO of the company, and he agreed with me that his time had come to take on a new role, and he became CEO of GenPharm. The first product we wanted to make in milk was lactoferrin, an interesting product which is produced in high levels in human milk and also in high levels in bovine milk very early on when the calves need to be fed. So, it probably has very strong antimicrobial activities and some other very interesting activities to transport iron from the outside to the developing animal. We felt that if you could produce human lactoferrin in milk of cows, it could be a very profitable product.

VI GLYCOGEN, INC., MARCH 1990-NOVEMBER 1991

Enzymatic Synthesis of Complex Carbohydrates

Heyneker: After six years at Genencor, I became a little antsy and I wanted to do something else. There was another opportunity which came through Genencor's doors. Roger O'Neill, who was a scientist at Genencor, had come back from a meeting where he learned about mammalian glycosyl transferases. These are enzymes which are involved in building complex carbohydrates on the surface of mammalian cells. If you look at mammalian cells, they are decorated with all sorts of different complex carbohydrates, and nobody really knows even today what most of those complex sugars do, what their role is. But we felt that those complex carbohydrates could be very interesting therapeutic targets. The idea was that once we cloned these different glycosyl transferases, we could make all sorts of combinations of complex carbohydrates, basically produce them by enzymatic means.

The only alternative is to make them by chemical means. I will not bother you with this, but making these by chemical means is exquisitely difficult, and to make them by enzymatic means is exactly the right way to do it. So here again was a great opportunity to venture into a new area, namely the manufacturing of complex carbohydrates, and look for pharmaceutical activities using enzymes which could be produced in high levels in filamentous fungi, a field that Genencor pioneered. It was not something for Genencor to do themselves. But as a spinout company, it was a great opportunity to enter this new area.

Hughes: What was the basis for believing that complex carbohydrates had a medicinal use?

Heyneker: That is a good question, Sally. There were not that many examples that they would have medicinal use. But from a philosophical point of view, one could deduct that complex carbohydrates must have a biological function because eukaryotic cells spend an enormous amount of effort and energy to decorate their surface molecules with all sorts of complex carbohydrates. If it were not for a specific biological reason, I think that they would have lost this ability over time.

Really it is remarkable. There are twenty or thirty glycosyl transferases which are expressed in different cell types at different times, which give you an opportunity to put all sorts of different combinations of complex carbohydrates on the surface of cells. We know that it has something to do with cell trafficking and those sorts of important biological processes. It was more on the premise that the carbohydrates must be doing something, and also based on the fact that those molecules were extremely difficult to make by chemical means, and therefore there was very little evidence that those molecules played a biological role. Here we had an opportunity to make these molecules by enzymatic means, really using the strengths that we had developed at Genencor, namely to make all of these types of enzymes cost-effectively at large scale. So, the idea was that we had buckets of enzymes of all these different glysosyl transferases and that we could mix and match and make all sorts of different molecules this way.

Sellout to Cytel

Hughes: Was anybody else trying to make carbohydrates enzymatically?

Heyneker: Well, there was one other company, which around the same time started roughly in the same field; it was Cytel. In the beginning, we were fiercely competitive with them. We had some leaders in the field assembled to help us, and Cytel had done the same. At the time we started the company, we were aware of them; they were aware of us. It was just a matter of time that we decided to join forces. So GlycoGen existed exactly six hundred days from the start to the day we sold the company to Cytel. [laughter]

Hughes: Why couldn't it have gone the other way?

Heyneker: It could have gone the other way. But Cytel had funding from VCs [venture capitalists]. They were farther ahead in their history. We had some very good technology and some strong patent applications.

Hughes: Did you license some of this technology from Genencor?

Heyneker: The contract with Genencor was that we had access to their technology for the complex carbohydrate field, that they would produce those enzymes for us, and in return they owned a significant amount of GlycoGen. It was a very good relationship, and I think that Genencor was very interested in it.

Hughes: Did you get to a product before GlycoGen was sold?

Heyneker: No, we did not. We focused on a molecule called sialyl-lewisX, which we felt was involved in cell trafficking. We had hoped that it would be an important molecule for immune regulation because it would influence the extravasation of leukocytes.

Hughes: What?

Heyneker: Extravasation means that those cells will pass through the wall of the vasculature and wiggle their way between cells to the area of inflammation.

We focused on this molecule to prove the technology, that we could indeed produce these types of complex carbohydrates by enzymatic means, and we made a lot of progress. We succeeded in that, but we felt it was in the interest of both parties to join forces and to become the leading complex carbohydrate company.

Co-Founder and CEO

Hughes: You founded this company?

Heyneker: Correct, together with Roger O'Neill.

Hughes: So you co-founded it.

Heyneker: Yes.

Hughes: This was the first time?

Heyneker: Right, for me.

Hughes: So what kind of thought process did that require of you?

Heyneker: I felt that it was an important opportunity, and I wanted to try it. I was probably naïve and did not understand all the challenges of being a CEO.

Hughes: Are you thinking in terms of the business/financial side of it? With the science you didn't have any doubts.

Heyneker: The science was the least of my worries. That was definitely an area that I could put my arms around. I knew what needed to be done; that was not a problem. I must say to run a company was definitely more difficult than I had anticipated and less fun. It was not really my strength. After this six hundred-day experiment I told myself not to become a CEO of another company.

Hughes: It didn't stop you from becoming a founder.

Heyneker: That's different.

Hughes: Elaborate on why you came to that decision, what you found about the CEO role that you didn't think was compatible.

Heyneker: I was inexperienced in this field. I did not understand what it takes to raise money—also the discipline that you need, the focus. Organizational skills are not my strong suits. I would much rather be a team player and focus on the things I'm good at and help people who are good with organizational skills to build a company.

Hughes: Are you good at selling an idea to nonscientists?

Heyneker: I could be but I have to believe in it.

Hughes: And you didn't?

Heyneker: Oh, in the case of GlycoGen I absolutely believed in it. We could sell our concept. There were a lot of people who were definitely interested in the concept. Don't forget that we started this company in 1990. It was not a very good time for biotechnology. It was definitely quite difficult to raise money and to find money.

Hughes: Were you the one who was doing that?

Heyneker: As CEO, you are responsible. We hired a business development person, Nancy Kames, who was extremely good in doing the operational aspects. She deserves a lot of credit to get the company where it went. The fact that we sold the company six hundred days later doesn't mean that we were unsuccessful. We felt that it was in the best interest of GlycoGen as well as for Cytel to merge. We had some complementary skills, a complementary patent portfolio, and we thought that together we could strengthen the concept.

Hughes: Were you relying on your friend Jonathan MacQuitty for business advice?

Heyneker: Yes, if necessary, but I think that he was definitely inundated. It was also his first time to be CEO.

Hughes: He had his own problems. Did you find yourself as CEO thinking back to what you had seen of Swanson's management style?

Heyneker: Sure, it didn't escape me.

Hughes: Of course, the circumstances were different.

Heyneker: Sure, it's hard to compare. But what I did like about GlycoGen was the novelty of the concept. It turns out that even today people are not finding many applications for complex carbohydrates. We have not found many medicinal leads. It is very surprising. I must say that the concept for me is just as valid today as it was then. I really feel, from a technology perspective, it was definitely a solid way to make these molecules.

Hughes: Weren't you cutting off quite a bit to chew? As you were saying, it was new for you to be in a CEO position, but you also chose a branch of science where the applications were unclear.

Heyneker: Absolutely. I knew it was a risk, and the people who put money in the company knew that as well. At that time there were no examples of what to do with complex carbohydrates. It was all based on the premise that nature spends a lot of time making these complex carbohydrates.

Hughes: Do you consider yourself to be a risk taker?

Heyneker: Yes.

Hughes: Do you want to say more than that?

Heyneker: Yes, I am definitely a risk taker.

Hughes: Why do you take risks?

Heyneker: A good question. Sometimes I ask that myself. It is probably the challenge. I love to push the frontiers of science and look for novel opportunities. If you don't take risks, you often don't get rewards. Perhaps I need the excitement; I need the rush. It is important to try new things.

Hughes: I believe the longest time you have been at a company was at Genentech, and that was only six years.

Heyneker: Well, six years at Genencor.

Hughes: True, but six years max, and you get bored.

Heyneker: Did I say that?

Hughes: No, I said that, drawing from the evidence.

Heyneker: No, my leaving Genentech to go to Genencor was not out of boredom, and, again, I didn't feel that I was leaving Genentech.

Hughes: I stand corrected.

Heyneker: After six years at Genencor, where the research group was extremely good and self-motivated, they didn't need a person like Herb Heyneker.

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Heyneker: I felt that the new opportunities at Genencor were limited. We had our hands more than full, developing the portfolio products. We were not really looking at new products. We did try our hands at coming up with an enzymatic process for aspartame, the artificial sweetener. I was not really making a contribution the way I wanted to make a contribution. I felt that by going to a company like Glycogen, I could make such a contribution.

VII VISITING SCHOLAR, DEPARTMENT OF GENETICS, STANFORD, JANUARY 1992-JANUARY 1994

Return to Academia and a New Method for Sequencing DNA

Hughes: Are we ready to move to a discussion of Stanford?

Heyneker: Yes, Stanford. I recall that after GlycoGen was sold, I thought, what's next? I felt that I needed to recharge my batteries. My personal life was difficult. Pauline and I had split up. I wanted an easier life, a more structured life, going back to science. I decided to visit Tom Brennan who had moved from Genencor to Stanford University, in the department of Dave Botstein. I saw that he was quite content there, doing very interesting stuff. I asked him if I could join him. He was a visiting scholar there, and I thought, what does it take to become a visiting scholar? It didn't take much. I had to see Dave Botstein, who I knew from my Genentech days, and we were very good friends. David Botstein was kind enough to invite me to be part of his group at Stanford as a visiting scholar, which gives you an enormous amount of flexibility.

Tom was working on several things, and I joined him. He came up with a clever idea to sequence DNA, which was related to the Maxam-Gilbert sequencing technique. But we had to hope that we could sequence out farther, meaning that we could sequence a couple of thousand base pairs, instead of in the high hundreds. It would have been a great improvement. It was an interesting idea where you needed enzymes and oligo[nucleotide]s— all of the things I was comfortable with and I understood. So, I decided to reduce this concept to practice, and I must say that it was very therapeutic for me to be at Stanford. It is good to be around scientists, to be in an academic setting where problems are discussed. It was déjà vu, and it was good.

Hughes: The déjà vu, being UCSF?

Heyneker: Yes, UCSF and also my earlier days in the Netherlands. After trying my hand at being a manager and a CEO, I went back to the bench. You asked before if I missed bench work. Yes, I did, and here was an opportunity to get back to the bench, and I did, and I enjoyed it.

Tom Brennan's Method for DNA Synthesis

Heyneker: While I was working on this sequencing by ligation technology, Tom Brennan was working on technology to synthesize DNA on a very small scale. He had some very forward-thinking, state-of-the-art ideas.

I should say some more words about Tom Brennan. He is a medicinal chemist, an extremely smart, self-made man, with a lot of knowledge about technologies outside chemistry per se—a very broad-based innovator. He was developing very fascinating technology. Being side by side with him, discussing these issues, really invigorated me. He also made me use a computer and get my email set up and come into the twentieth century. I had avoided this for the longest time. It had not been really necessary, but in 1990 it became really necessary, and I became thankful that he did this.

Hughes: You didn't need the computer for your science? You weren't using databases?

Heyneker: No, it helped me to do my own administration. I lived in an apartment in Palo Alto. I could bicycle to work, which I most often did. The weather was exquisite. I could come and go whenever I wished. It really helped me to calm down a little bit.

Colleagues in the Department of Genetics

Hughes: How much contact did you have with the Department of Genetics as a whole?

Heyneker: Quite a bit.

Hughes: Were you going to seminars?

Heyneker: Yes, I enjoyed them enormously.

Hughes: Do you keep alive ties with the department at Stanford?

Heyneker: Well, definitely with David Botstein and also Ron Davis I see quite often now. At the time I was there, Ron was in the same department as Dave Botstein. Also, Stan Cohen was there, so I strengthened my ties with him and with Annie Chang who is still his technician.

Hughes: Well, she has a Ph.D. now I believe.

Heyneker: Right. It was interesting to reestablish those ties, but it didn't last that long. I still had the bug of trying to mix science with business.

VIII PROTOGENE LABORATORIES, INC., JANUARY 1994-APRIL 1996

A Prototype Machine for DNA Synthesis

Heyneker: Tom Brennan in his project to synthesize DNA on a very small scale built a prototype machine, a proof of concept machine. He didn't synthesize on that small a scale, but still he built a machine which allowed you to synthesize different oligos in a ninety-six well format, and that was a very interesting DNA synthesis machine. It was an order of magnitude better than anything that was on the market.

Hughes: In what way?

Heyneker: Well, in the way of parallel synthesis of oligos. It was clear that oligos were playing a more and more important role in molecular biology research. Every time you want to amplify a certain piece of DNA by the PCR [polymerase chain reaction] method, you need two oligos as primers for your reaction. Also, more and more people did experiments in parallel: they wanted not just to look at one fragment; they wanted to look at hundreds of fragments at one time to do comparative studies, so you needed lots and lots of oligos. Really the chance started in the early nineties and is still going on.

Tom Brennan and I realized that we were sitting on a machine that could be very valuable as a research tool, and we decided to build a business around it—not a business to sell those machines, but a business to make oligos in large quantities and sell these oligos to the research communities much more cheaply than they were currently available, and thereby boosting the need for oligos. So, we did. We started this company, which we called ProtoGene, around the ninety-six well DNA synthesis technology. We hired a business development guy, Bob Molinari, who became a co-founder. So, here we were, three guys starting this new company.

Hughes: How was the business climate in January, 1994?

Heyneker: Much better.

Hughes: How did you find Molinari?

Heyneker: I can't recall.

Hughes: So, tell me how it went.

Heyneker: We hired a young lady; her name was Kim Ha. She was applying for a job at Stanford, and we got hold of her CV. She was very dynamic, very enthusiastic, and we hired her fresh out of Stanford, although she did not have any experience in DNA synthesis. But, I think that she was a very good hire, a very dedicated person, incredibly hard working. She basically learned on the job what needed to be done. She was absolutely instrumental in helping us to get the business up and running. We needed to do several things: we needed to build a DNA synthesis machine, and we needed to optimize the DNA synthesis. It was a real challenge to do so.

Hughes: You three were actually going to build the machine, or were you going to contract out?

Heyneker: It was Tom Brennan's baby. He was the engineer of the machine.

Hughes: Does he have an engineering background?

Heyneker: No, not directly. But by assimilation, he has a very good grasp of it. So, I was the chairman of the board, and Bob Molinari was the VP of business development, and Tom Brennan was the CEO/CTO. It was literally a mom-and-pop organization.

Life Technologies Takes a Stake

Heyneker: We raised some money from Life Technologies, and they took a 20 percent stake in the company.

Hughes: Did you do that cold? None of you had prior ties with Life Technologies?

Heyneker: No, we did not have particular ties, although what happened was that Stan Cohen was an advisor for Life Technologies, and he mentioned to them that we were building this interesting DNA synthesis machine. Mark Berninger came to check out this machine, and I knew Mark from other interactions—great guy. He realized that we were sitting on a gem and that this might be the entry for Life Technologies to get into the oligo business. They had been looking at the oligo business, which was in the hands of mom-and-pop shops, and they saw the opportunity only if they could do this on a very industrial scale. With the machine Tom was developing, they saw the opportunity to get into the oligo business in a very significant way, in a very industrial way, because we could make hundreds and hundreds of different oligos per day. We could probably make two hundred oligos per day, per machine, and we were building several machines.

The Microchip Market

Hughes: How is this tying in with what else is going on? For example—and I don't know when Affymetrix was founded, but it was around by then—would they have been interested in your oligos?

Heyneker: No, not really; they had a different format.

Hughes: They had the [micro]chip?

Heyneker: Well, they were building the chip then.

Hughes: Didn't you have a chip eventually?

Heyneker: Eventually, yes. We wanted to provide the research community with oligos for all sorts of purposes, mainly for PCR [polymerase chain reaction] purposes.

Hughes: I'm trying to find out what other technologies were out there.

Heyneker: It was the beginning of this chip business

Hughes: But you weren't thinking that chips were a possible secondary market?

Heyneker: Absolutely, we were thinking that. To immobilize these oligos on a piece of glass in different locations was basically the early way the chips were being made, either using synthetic DNA or using cDNA fragments. Okay, you make a PCR product, and you lay down the oligos directly. That was just the beginning, and it became a major application over time. So, the challenge was to build a robust machine. After a half a year, we had something which was really working. I remember that Kim Ha and Tom Brennan and myself spent many sleepless nights making oligos. If something went wrong, we had to start our synthesis over in the middle of the night because we promised products to the customer. It was absolutely a school of hard knocks to really make this industrial grade.

Hughes: It was just the four of you?

Heyneker: We hired another technician, so it became a six-man operation eventually, and we made a lot of progress.

Sellout to Life Technologies

Heyneker: At one point in time, Life Technologies realized that to let us do the work and they would do the marketing and sales of our product was not satisfactory. They proposed to buy out the whole business from us. We came up with the right price, and we sold the whole business lock, stock and barrel, to Life Technologies. It was two years later, in 1996.

Hughes: You had no misgivings?

Heyneker: None whatsoever. It was incredibly exciting to build the business. But to run the business on a day-to-day basis was a little bit boring and very aggravating because one of the selling points for Life Technologies was that we had a very short turnaround. So if anything went wrong with the machine, we were out there remaking it. So it was time-consuming; you needed very dedicated people. That's why hiring Kim Ha was such a fantastic hire. She really was a go-getter, really nice.

Hughes: Plus, it was a different business for you. You were selling an instrument.

Heyneker: It was really an oligo business, selling the product to customers. We made a limited number of machines, and we never wanted to sell the machines. We felt that it was much more beneficial to sell the product than sell the machine. Also, the time had come that individual labs did not want to be bothered with synthesizing their own oligos. If you know the process, the chemistry is extraordinarily harsh. If you don't do this on a regular basis, there are lots of potential problems. To make your oligos in the lab using a DNA synthesis machine which was sold by ABI or other companies was really a drag. The time had come that people would order oligos and have nothing to do with all the problems around them.

Hughes: Is that indeed what happened?

Heyneker: Life Technologies had such a fantastic marketing arm that they could present their oligos to a large audience. It really took off very well, and I'm proud to say that Life Technologies became the number-one oligo business in the world, thanks to that machine.

Hughes: I read that the technology was somehow connected with Lawrence Berkeley Laboratory and Stanford University.

Heyneker: Tom worked first at Lawrence Berkeley and then came to Stanford.

Hughes: Where is the market for oligos nowadays?

Heyneker: Oligos are indispensable in any type of molecular biology, especially since oligos are now the preferred method to make chips. You synthesize your oligo, which represents the sequence of a gene. I will come back to oligo synthesis, because at Eos I built a next-generation DNA synthesis machine which is based on a completely different methodology. I sold that for a second time to Life Technologies.

Hughes: All right, let's stop there.

IX EOS BIOTECHNOLOGY, INC., MAY 1996-FEBRUARY 2003

Array Technologies, Inc., a Predecessor

Foundation and Facilities

[Interview 12: July 10, 2002]##

Heyneker: After I left ProtoGene, I wanted to start another company. I had some ideas I wanted to carry out, and I wanted to be involved with the genomics revolution. My humble contribution should be to provide products and services to the genomics research community. I had an idea to build a highly parallel DNA synthesis machine, which allows one to make oligonucleotides, small pieces of DNA, at a very cost-effective rate. If you want to use the oligos to put on arrays and make so-called DNA chips with them, a prerequisite is to make these oligonucleotides very cost-effectively. So, I wanted to build this machine and to convert this idea into reality. We had some other ideas of what sorts of services we could run. For instance, an original plan was to sell these chips.

So, I started this company called Array Technologies. I found some space on the corner of El Camino Real and Page Mill Road in Palo Alto. You would think this was the most premier and best address on the Peninsula. However, at that place was a dilapidated building, and in that building was a biotech company. Its name escapes me. I found it by accident. I was walking and was interested what was in that building. I found that it was occupied by this biotech company, so I knocked on the door, entered, and had a very engaging discussion with one of the principals there. I asked him if there was by any chance some room available, which there was. For next to nothing I could rent space in that building at a wonderful address. It was something like fifty cents per square foot per month.

Hughes: Why was he willing to rent to you?

Heyneker: I think that I came as a godsend because his not-for-profit organization was running out of money. So to have a tenant who would foot some of the bill was very attractive.

Partnership with Steve Clark

Heyneker: I started Array Technologies with some of my own money, and I attracted a partner, Steve Clark, who was an engineer out of Caltech, to build this machine. Unfortunately that relationship turned out disastrously. We went in as sort of fifty-fifty partners, but the relationship didn't work out at all. I don't want to go into details, but it was very unpleasant in the end, and we basically parted ways.

Hughes: Did that mean that the machine didn't get developed?

Heyneker: Well, Steve was very much involved in building the machine. For instance, he built such a mammoth machine that it couldn't get out of the building. So, he had to disassemble it to get it out of the building. Well, I found that unacceptable for a Caltech-educated engineer. There were more things which I don't want to go into. So, that first start of the machine was really not something we wanted to continue with.

Indexing Technology

Heyneker: I acquired indexing technology out of ProtoGene. It was technology that I became very enamored with—a technology out of AECL, Atomic Energy of Canada, Limited. I was very enthusiastic about the technology because this allowed one to dissect the human genome. [tape interruption] So, another leg of the stool on which I wanted to build Array Technologies was this indexing technology. I found that technology at a meeting where I met with Paul Unrau, the inventor of this technology. As a matter of fact, it was in Nice, France. I still remember it vividly. He presented a poster, and I didn't understand it in great detail. So we ended up having some beers at the bar, and all of a sudden it dawned on me what the potential of this technology was.

Hughes: He hadn't seen its potential?

Heyneker: Well, he understood it, too, but in Canada it was not so easy to commercialize it. I helped him to get a U.S. patent on this technology. I spent a lot of time and effort to get it that far, and we were successful. So, the indexing technology was now protected. I was very excited about it because this technology allows you to dissect a very complex genome, like the human genome, into sufficient parts that you really can do genomics research on it. Let's not forget, this was done in the days when the sequence of the human genome was not done. This is important, because once the genome was sequenced, the indexing technology became to a large extent obsolete. Because once you know the sequence, there are more powerful technologies to look at the expressed genome, like for instance DNA chips.

Hughes: What does the indexing do?

Heyneker: Indexing allows you to look at DNA fragments, fragments you obtain by cutting DNA with a type-2 restriction enzyme. The beauty of this type of restriction enzyme is that it leaves sticky ends, but they are not always of the same sequence. If you digest DNA with a type-1 restriction enzyme, like EcoR1, which is Herb Boyer's enzyme, you always get sticky ends which have A-A-T-T at the overlaps. But if you digest with a type-2 enzyme, you get ends which are determined by a sequence which is internal to the DNA fragment. The sticky ends have all possible sequences. So if there is a four-bases overlap, on each end you have 4^4 or 256 possible outcomes. On the other end, you have also 256 outcomes. Since there are two ends to each fragment, the chances that you have two fragments which have exactly the same ends is one in 32,000. So, this technology allows you to dissect all these fragments in 32,000 different bins, and that is extremely powerful if you want to do genomic analysis. I am still very excited about it, but again once the whole sequence is known, there are other technologies which are easier, more powerful, more parallel. Therefore the indexing technologies have become obsolete, at least for us.

A DNA Synthesis Machine

Hughes: You said it is a highly parallel synthesizing machine. What do you mean by "highly parallel"?

Heyneker: What I mean by parallel is that you can do a lot of things at the same time. For instance when it comes to DNA synthesis, which I call parallel synthesis, we could synthesize hundreds of different oligos at the same time. When I talk about parallel with regards to genomics, on a chip you can analyze tens of thousands of different genes at the same time. It's jargon in our circles to describe that you can carry out many analyses at the same time.

Hughes: Okay. So the machine was going to be one of the bases for Array Technologies?

Heyneker: The machine was another base. I discussed this indexing technology with Lynx Technologies, and David Martin was the CEO of Lynx. He was quite interested in this indexing technology because it fitted that company very well.

Hughes: Which was doing what?

Heyneker: They were also looking at expression analysis to see what sort of pattern certain cells expressed. They had some very clever technologies. So, Dave Martin was looking for a vice president of R&D, and he was interviewing me to become part of Lynx, but I didn't like the feel of Lynx. When I interviewed, it was not my cup of tea, which I told Dave. Dave Martin and I go back a long way. We know each other from UCSF, and later from Genentech. He was fine with it.

Hughes: Do you care to say what you didn't like?

Heyneker: It was the way it was run. Sam Eletr was the founder of that company. It was nothing against Sam Eletr or Dave Martin, but it didn't feel right for me. That is not a judgment against the company; it is just my personal feel.

Eos Biotechnology

Foundation with David Martin

Heyneker: So, surprise, surprise. I would say three or four months after I explained the indexing technology to Lynx and after they interviewed me to hire me, I got a call from Dave Martin, telling me that he had left Lynx. As a matter of fact, he said, "I have been fired." I said, "Dave, this is a perfect opportunity to carry out the dream of what you can do with this indexing technology and with this DNA synthesis." So, we got together, and we decided to go on together. We changed the plan. Instead of providing services to the genomics research community, we decided to use these technologies for our own advantage, basically forward integrate and become more the beginnings of a genomics/ pharmaceuticals company. So, we realigned the company, and we wrote a different business plan, and we were very successful in raising some early money. We changed the name from Array Technologies to Eos.

A Second-generation DNA Synthesis Machine

Hughes: Why?

Heyneker: Because we did not want to reveal in the name what the company was going to do. We were no longer a company which was based on arrays; we were becoming a pharmaceutical company. So I think it was a smart move to change names. Array Technologies, which was undercapitalized, had to get rid of a founder—well, sort of rebuild the whole thing on a much more professional basis, which I probably could not have done on my own. But together it was a good move.

So, we set out, Dave Martin and I, to really develop the indexing technology as well as continue to build a prototype machine based on my idea for highly parallel oligosynthesis. Then we got wind of another company that also wanted to occupy similar space we were occupying. That was sort of a spin out of Affymetrix and DNAX, spearheaded by David Mack from Affymetrix and Richard Murray from DNAX. They wanted to build a genomics company using the Affymetrix chip platform. So, we got together with those two gentlemen, and we decided to restart Eos, absorb their company, and make them co-founders of the new Eos with a larger vision. That really is the basis of what Eos is

today.[1] As a matter of fact, we did build a DNA synthesis machine, which turned out to be highly successful. It was extremely gratifying to me to see this machine see the light of day. Indeed, it was doing what I had hoped it would do.

Hughes: Was it related at all to the earlier one?

Heyneker: No, it was not really related to the aborted one. I think it was a much more pragmatic design, but it was still on the same principle.

Hughes: Were you actually selling the machines?

Heyneker: Well, what happened is that we built this machine for in-house use so that we had a source of oligonucleotides, so that we could make our own chips at Eos. We used those chips in parallel—perhaps I should not use the word parallel—together with the Affymetrix chips to look at different tissues and different cells and [their] expression profile to learn something about [their] physiology or pathology. For instance, we were—and we still are—highly focused on cancer, understanding cancer cells in relation to normal cells. The technology we are building is extremely powerful to give a snapshot of the differences between normal cells and cancer cells. From these differences, we wanted to develop drugs.

Hughes: Are these mainly surface proteins?

Heyneker: Right, we were focusing on surface protein. The idea is to make antibodies against these surface proteins, which are unique for cancer cells. We have an immunotherapeutic approach, very much like Herceptin, which was pioneered by Genentech.

Hughes: It seems to me that you were bringing together elements of your past research—your longstanding interest in antibodies and in oligo synthesis. Does each of these generations build somewhat on the last?

Heyneker: I would say, of course. You use the knowledge from the past to improve.

Now, what Eos did—to finish up on the DNA synthesis machine—we became very proficient in making arrays based on this DNA synthesis capability. But at one point in time, it didn't make sense to have two platforms side by side. The Affymetrix platform was really more suited to look at the entire genome and to get a comprehensive picture of what differentiates normal cells from cancer cells.

Hughes: Why is that?

Heyneker: Because we did a lot of work at Eos on an Affymetrix chip to build a very proprietary chip which had the entire human genome on one chip. You can't get any better than that. That was really very difficult to do on an oligonucleotide-based chip—at least on a spotted-array-based chip.

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1. In April 2003, Eos was sold to Protein Design Labs.

Web Oligos, Inc.

Heyneker: So, we decided to spin out this oligo business, and we spun out a company called Web Oligos. Clearly, it was in the days that everything you could do over the web—sell things over the web—was not only fashionable but very efficient. So, we started this company and—

Hughes: "We" is you and David?

Heyneker: Well, me basically. I was spearheading it as a spinout from Eos. We were trying to build a fully integrated company, which means that we had the capability to synthesize the oligos, and we needed a business development effort and a marketing and sales effort. So, while that was going on, Life Technologies got wind of our activities, and they visited us and saw the machine and what we could do, and they became very excited about it. To make a long story short, they bought the entire operation from Eos, which is sort of ironic, because this is the second time that we sold an oligo business to Life Technologies.

Hughes: That's right.

Heyneker: I think it was a very attractive sale—attractive for both parties, not only for Eos but also for Life Technologies. The machine we built was clearly superior to anything which was out there, and I'm very excited to say that Life Technologies is switching their complete business to this machine.

Hughes: How long ago was the sale?

Heyneker: We sold this, I think, in the year 2000. It was a big success. The machine we built was really a very industrial machine, very robust.

Employees

Hughes: How much are you involved with the engineering of these instruments?

Heyneker: Not that much, but I learned an enormous amount. I was sitting in with the engineers and with the people who did the design. I should mention here the name of Victor Simonyi of Berkeley BioWorks. During the development of this machine, we became very good friends, and I must say that Victor Simonyi is a great mechanical engineer and a great human being.

Hughes: Are you on the board?

Heyneker: No, but I am advising them.

Then at Eos, we had several people whom I'd like to mention. One is David Steinmiller who is in a Stanford master's program.

Hughes: In engineering?

Heyneker: Yes, especially electrical engineering and software. He did wonderful things to make this machine work. Not only do you need mechanical engineering these days, but you need a software program to make this complex machinery talk to its different parts. Then there was Kim Ha. Both Steinmiller and Kim Ha came from Array Technologies, were very early hires. Kim Ha who, [as I mentioned,] also worked at ProtoGene and was very instrumental in helping to get ProtoGene off the ground, played a major role in making sure that this new instrument was working.

Dave Steinmiller, again, did the electrical engineering and software engineering, so it was a wonderful team. It was basically my idea, but without these people's help, it would have gone nowhere. This clearly would only work in a true collaboration. I found it a fantastic experience. It gave me a new perspective. Those were good days.

Hughes: A new perspective?

Heyneker: I was working with a different group of people; I had never worked with engineers before. I had worked with fellow molecular biologists and cell biologists and geneticists. This was a completely different field, but a field that really attracted me.

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Hughes: What about the identification of the target cells? Was Eos doing that?

Heyneker: Absolutely. It was and still is our mainstay. We are a company which focuses most of its efforts on cancer. I think that we have a very efficient technology in place to identify surface markers which are specific for all sorts of different cancer cells, like colorectal, prostate, lung. We have done them all. We have a collection of surface markers which are quite specific for cancer cells and which do not occur in any normal tissue.

Evolution of Antibody Therapeutics and Diagnostics

Hughes: Is the collection unique?

Heyneker: Well, you never know. We are definitely a frontrunner in this area. Eos used the Affymetrix chip technology to its advantage. We have built a very valuable collection of surface markers and therefore of potential drug targets. Now we are talking about very recent developments at Eos, moving forward with the company by using these drug targets or a subset thereof and developing antibodies against them with the goal to develop antibody therapeutics. So, the emphasis on finding the targets is shifting to an emphasis on making high-affinity therapeutic antibodies. That's an exciting and a necessary development for Eos to become a successful company.

Hughes: How closely had you been following antibody technological development since the time of your research at Genentech? I imagine there were huge leaps in knowledge.

Heyneker: Good question. There was a big dry spell between, let's say, the development at Genentech of antibody technology and then the current use of antibodies for therapeutic purposes. The dry spell came when I was at Genencor and also at ProtoGene, et cetera. But that antibodies are very powerful therapeutics has been recognized in the last, well, six years. It was a false start. In the eighties, there were some very disappointing results with antibodies, and a lot of people lost faith in the possibility to use antibodies for therapeutic purposes. But after this initial disappointment, currently there's an enormous amount of hope and promise for antibodies in a whole variety of therapeutics—not just cancer therapeutics, but lots of other therapeutics.

Hughes: Technologically, what happened?

Heyneker: We started to understand antibodies in much more detail. Also, we understand in much more detail the antigenicity aspects of it. Also there was some sort of unfortunate choice in the beginning. People wanted to develop antibodies against septic shock, which is a particularly difficult set of diseases, as we know now. It's much more complicated than we had originally anticipated, so it was an unfortunate choice, and it didn't work. There were some adverse reactions. People became disenchanted.

Hughes: Was septic shock ever a target for Genentech?

Heyneker: Yes, it was. It is a huge unmet need. It is a very difficult target to really put your arms around.

Hughes: In parallel, there was always the diagnostic use of antibodies, which came much earlier in the history.

Heyneker: Of course. Diagnostic antibodies were around before even cloning became fashionable. Generation of polyclonal antibodies by injecting rabbits or whatever animal with an antigen was common practice, I would say, from the fifties. Lots of assays were and still are dependent on antibodies because of their exquisite sensitivity and specificity.

Hughes: Some of the early companies, like Hybritech and Monoclonal Antibodies and maybe even Centocor—weren't they largely based on diagnostics?

Heyneker: I don't think diagnostics was really the ultimate goal of these companies, because a successful therapeutic antibody is much, much more valuable than a diagnostic antibody. The proprietary nature, the difficulty to develop a therapeutic versus a diagnostic—we're really talking about an order of magnitude degree of difficulty. I think the goal really was a successful therapeutic antibody. Herceptin for Genentech is more profitable than any of the other recombinant DNA products. Also for Centocor, since you mentioned that company, [they] were very successful in the end in developing therapeutic antibodies. They were bought out by Johnson and Johnson for a nice price. So, the Holy Grail definitely was and still is therapeutic antibodies. Hundreds of different antibody applications are in front of the FDA. I think antibodies will continue to play a major role in novel therapeutics.

Hughes: Aren't antibodies one of the bases of people's faith in the future productivity of biotechnology, that it's largely on the antibody-based products that people are hanging a lot of their expectations? "Antibodies, Promising Products for Biotechnology"?

Heyneker: Yes, the reason is that there are now a number of examples that they work. We have learned an enormous amount about how to manufacture them, how to make them clean enough that the side effects are minimized. Therefore, you don't have to start from scratch with the next antibody. So, there's this body of knowledge on which you can build. So the next and the next antibodies take advantage of this. It is relatively easy to get an FDA approval for an antibody, compared to, let's say, small-molecule drugs.

Hughes: Why?

Heyneker: Because there is a lot of commonality—manufacturing process, safety profile—which is for all antibodies very similar. That's not to say that certain antibodies can't have very severe and perhaps devastating effects. But the underlying mechanism of how to produce antibodies and how to purify them is the same basically for every antibody. You still need to do, of course, careful phase one, two, three clinical trials, but the FDA is getting very comfortable with antibodies as therapeutics. It's really a class of molecules, and as long as the class is the same, approval gets more straightforward: Show me that it works, and show me that there are no adverse effects. But besides that there are not that many other questions the FDA will ask. Safe and efficacious—that's all. That's one of the main reasons that antibodies are very popular currently, and why there is a lot of emphasis on antibody therapeutics.

Hughes: Well, I looked at the Eos web site. We touched on the company's strategy. You've mentioned identifying pathogenic cells, finding disease-specific targets in the genome, then building the antibodies. The fourth thing according to your web site is entering into collaborations to exploit other opportunities.

Heyneker: Once you have identified targets for intervention, there's always the opportunity that a small molecule can take the position of an antibody. If that's the case, a small molecule like a true drug probably will win. It's much cheaper to manufacture, and it's probably orally available. There are a lot of advantages of small molecules over antibodies. So I think you should always keep in mind if you use an antibody therapy against a target that competitors who develop small molecules against the same target probably will have an edge in the long term. So, we have to be aware, and I think it is very prudent to pursue collaborations with people who are experts in small-molecule [drug] development.

Failed Merger with Pharmacopeia

Hughes: Are you actively doing that?

Heyneker: We're trying. For instance, definitely one of the reasons for our attempt to merge Eos with Pharmacopeia was [because] Pharmacopeia are experts in small-molecule libraries, and they wanted to take advantage of that opportunity to develop small-molecule drugs against some of our targets.

Hughes: And what happened with the attempt to merge?

Heyneker: It failed miserably, and I'm very bitter about it. I think it would have been good for Eos; it would have been good for Pharmacopeia.

Hughes: What was the basic problem?

Heyneker: You never know exactly. The deal was probably too rich for Eos—at least that was the way it was perceived by Pharmacopeia shareholders. There was one party that was particularly opposed to this deal. They were a very big investor in Pharmacopeia. They held, I would say, between 10 and 15 percent in Pharmacopeia, and they didn't like the deal. Joe Mollica, who is the CEO of Pharmacopeia, could not alleviate their concerns, and they became very antagonistic and were very active in the proxy fight. And we failed. But it was not something that should have happened. It should have been managed, in my opinion, much more professionally.

Patenting Genes at Eos and Elsewhere

Hughes: The web site also says that Eos has filed seventy-five patents, and I quote, "…encompassing over three thousand genes associated with specific disease processes." Now, what does that actually mean? You're not patenting a gene per se, are you?

Heyneker: Well, we may. I don't think that I can or want to reveal our patent strategy here.

Hughes: Oh, I didn't mean to address a taboo subject.

Heyneker: I know. Probably that's the first cut which came out of our Affymetrix chip screen. Of course, there are subsets of those which have our particular attention. I can guarantee you that we are not pursuing all three thousand genes.

Hughes: I would think not.

Heyneker: We are focusing on a very small subset of those [genes] which have very interesting profiles. But once you find certain specificities, I think it is prudent, and you are obliged to your shareholders, to patent those genes and molecules which have a chance to be of value.

Hughes: What does that mean for other individuals or companies that wish to work with those genes?

Heyneker: Good question. If we have filed first, they probably have to knock on our door to further pursue that. There are several ways to look at patents. They give you protection. They are bargaining chips, because in this world of genomics, a lot of people have patents, and I am convinced that there are a lot of overlapping patents. Patents are being used and will [continue to] be used as trading and bargaining chips to carve out a field. So, we are participating in that process. We are not the only ones, that is clear; however I think we have a subset of genes that are very exciting and interesting.

Hughes: How do you feel about patenting genes that for the near future you have no intention of working on?

Heyneker: [pause] I don't think that it matters much how I feel about it. It matters more that this is currently the trend. You can either agree with this or at least follow this trend, or you can rebel. But I'm not sure if rebelling against it will get you anywhere. I'm not saying that I agree with all aspects of this, but I am not an expert in the field of patents. We find ourselves as a research community in this predicament that we have to file where we feel we have made an invention.

Hughes: The invention is the isolation of the gene?

Heyneker: Well, not just the isolation. It's more the identification of a gene and associating that gene with a disease. That is, of course, a patentable occurrence.

Hughes: I'm skating on thin ice here—

Heyneker: Well, I'm on thin ice, too.

Hughes: Some years back NIH said that it was going to patent genes that had been isolated and characterized but had not been linked to a function or to a disease. There was a tremendous furor.

Heyneker: Yes, but NIH does not have an authority here; patentability is determined by the patent office.

Hughes: Oh, I know that. NIH was going to apply for patents through the usual process.

Heyneker: No matter what, whatever policy, there will be an outcry. Personally, I might have my own opinions about this.

Hughes: Which you are not going to reveal here. [laughs]

Heyneker: That's correct.

There are a lot of things which have to do with the law which I am not an expert in. I might have my opinions, but so what?

Changes in Patenting in Biology

Hughes: Have you ever looked back over the changes in this area that have occurred in your professional life?

Heyneker: Yes. When I started in Herb Boyer's lab, patenting of biological research was very unusual. It was done on a routine basis in physics and chemistry, but biology was a little behind. With recombinant DNA technology, all of a sudden biology became a commercial science, while before it was basically science for the sake of science.

Hughes: Without necessarily a practical end?

Heyneker: Right, exactly. Recombinant DNA technology opened the doors to the commercial aspects of [biology], and rightly so. It was such a new field, and it moved so fast that I'm not sure that the patent office was really in control of the process. I think that the patent office in the United States is in a difficult position. It's understaffed; it's very hard to attract the quality people who can really understand the issues and can make decisions. I'm appalled that America is not paying more attention to this and giving the patent office more money so that they can do the job well.

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Heyneker: It is in the best interest of the United States and its economy to have a professional, coherent patent office which can make decisions which are understandable and not based on the luck of the draw. Currently, you can be lucky and have a patent officer who looks at your patent and understands it and is very cooperative. Or you can have somebody who just doesn't get it, who's not interested in it, and has made the decision that he or she is not going to patent it. There is no process for justice here—luck of the draw. It's terrible. I can guarantee you that I'm not the only one who is complaining here. It is a mess. [Patenting] is so critical to protect America's intellectual property, and America can only stay ahead of the game by sponsoring new technologies.

Heyneker as Scientist and Technologist

Hughes: What do you say when someone at a cocktail party asks you what you do? In other words, how do you identify yourself to the outside world?

Heyneker: Well, I probably still identify myself as being a scientist.

Hughes: Is that how you think of yourself?

Heyneker: Well, less so than during the times that I was a bench scientist. But I use my scientific skills and knowledge and understanding to pursue business.

Hughes: Is what you are now a scientific entrepreneur/businessman?

Heyneker: Yes—

Hughes: Or technologist?

Heyneker: Technologist—I like that. I think I bring technologies to the attention of businesspeople. I feel that I'm bridging those two disciplines.

Hughes: Do you get the same satisfaction now that you did when you were doing bench science?

Heyneker: It's different. I think it gives me a lot of satisfaction to see a new technology being developed successfully. "Successfully" means commercially successful. I think it's

important. It also gives me some personal satisfaction that I identified something which is worth pursuing. I do miss simple things like through experimentation finding new clues. That is also extremely satisfying. I would say that my job evolved over time, sort of a logical extension. I was always from the beginning—as you know from our interview—excited about technology which can be applied especially for medical purposes but also for other technology purposes. So, from that point of view, I had it in me to be at this interface between research and business development.

I was extremely fortunate to be at a time in my life and my career that I was involved in the early development of a very important technology. It's very important to me, and I've thought about it a lot. I'm fortunate that I feel that I made a contribution, and you can't take that away from me.

Heyneker as a Team Player

Hughes: What contribution are you most proud of?

Heyneker: [pause] That's a good question. The reason why I can't find an answer quickly is that I feel that I was part of a team, and without the team, as an individual contributor, it's not so important. But I was good in assembling teams and finding complements so that together you could make a big impact. Perhaps my biggest satisfaction is that I have been part of lots of different teams, and the team quite often was very successful. It was not just luck and passive activity. I was proactive in finding the people who could help me be successful, and I wanted to make sure that any success belonged to the group or to the team—that's fun.

Hughes: Were you the individual with the awareness of how a group of people should work together, perhaps even moving the group in certain directions?

Heyneker: Well, yes. Perhaps I was not aware of it, but it sort of came naturally to me. Herb Boyer made me an enormous compliment that he felt that in his lab I really made a big contribution in putting the group together to work on a common goal. I don't think that I did that as part of a grand scheme or a deliberate plan. It was more like together you can move faster, and together you can move in more significant ways.

Hughes: So, before you came, individuals were working on individual projects?

Heyneker: Absolutely. That is still ingrained in the whole system here, because for your career you need to shine as an individual. Postdocs often have individual projects because that is their way through publications to show to the world that they are accomplished researchers. But coming from Holland, I didn't have to write grants. I didn't have to participate in this rat race, and therefore I could be much more relaxed about it and be more open and say, "Let's collaborate."

Hughes: Why did people follow you?

Heyneker: I think because it made a lot of sense. I am not saying that I am unique. But I had very little problem with being part of a team instead of being the primary researcher. I was very goal oriented. I loved to see something work or something accomplished, and that is still what I like.

Hughes: There must be something other than just nation of origin as an explanation. Axel Ullrich and Peter Seeburg came from Germany where the system of funding science I'm imagining was closer to the Dutch than it was to the American.

Heyneker: Correct.

Hughes: I would argue that personality or some other element was a factor. It's not enough of an explanation to say that it was because of your experience in the Netherlands.

Heyneker: Well, it helped. Peter Seeburg and Axel Ullrich and John Shine—we all could have done it. It helped enormously because approaching these guys was very easy.

The United States and the Education of Postdocs

Hughes: Why was it easy?

Heyneker: We had a commonality in trying to accomplish something. To answer your question in a slightly different way: UCSF has a premier medical school. It provided the opportunity for postdocs from all sorts of different countries to come together. This is incredibly powerful, and Stanford has that same sort of ability. Harvard has it, MIT has it. The top schools in America have this incredible ability to attract the best and brightest from all over the world. Once you have that name, once you have that system in place, it is almost self-fulfilling and self-propelling. I came from Leiden University, which has a good name in the world. We don't have a system that people from all over the world come to Leiden University to do postdocs, and there are very few schools in the world which have that ability. It's incredibly powerful to forge international relationships.

Hughes: What is it that these premier research universities in this country offer?

Heyneker: They are leaders in the field. Once you are a leader in the field, people want to come to you from all over the world. Therefore, new leaders are created, and therefore, the university or institute stays on top. It's an open-door policy. America is very good at inviting and giving foreigners opportunities to come and study and get educated. Don't forget that 60 percent of the Ph.D.s are obtained by foreigners. From that point of view, America has a very powerful, very smart system to attract the best and the brightest in the world. A subset of those will stay and will help America's economy. I'm very opinionated, and some things I don't like, but this is something which I admire America for. This aspect they did absolutely right.

Personal Priorities

Hughes: What in life is most important to you?

Heyneker: I think that changes over time. What is important for me today was probably not that important for me twenty or thirty years ago. I had different goals in life then. To be successful as a scientist and to be the first to invent and to make a name for myself—all that sort of stuff—was very important for me in my thirties and forties. It's much less important now. What is important now—at least from a scientific point of view—is to identify and find new technologies which will be the basis of a successful commercial enterprise.

But there are other things which are important in life besides your career—of course your personal life. Also that, I think, is changing over time. I've come to learn that family is very important, and I also came to experience that I couldn't keep the family together. They are intertwined. Perhaps you start realizing its importance when you can't take it for granted. I've been long enough in America that I can call it a life with all its ups and downs. I'm getting perhaps a little philosophical, but overall I'm very grateful; I'm extremely fortunate to participate in this new world of biotechnology.

Hughes: Thank you.

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Herbert L. Heyneker

Education

Post-doctoral Fellow, Dept of Biochem. and Biophys., University of California
San Francisco School of Medicine (Nov. 1975 – Oct. 1977).
Advisor: Prof. Dr. Herbert W. Boyer

Ph.D., Dept. of Molecular Genetics, University of Leiden, the Netherlands.
Thesis: Enzymes involved in the repair of DNA, damaged by ultra-violet light (Oct. 1975).
Advisor: Prof. Dr. A. Rorsch

Professional Experience

Founder and Chief Technical Officer — May 1996 – present
Eos Biotechnology, Inc. (formerly Array Technologies, Inc.)

Founder and Chairman of the Board — Jan. 1994 – Apr. 1996
ProtoGene Laboratories, Inc.

Visiting Scholar — Jan. 1992 – Jan. 1994
Dept. of Genetics, Stanford University, School of Medicine

Founder and CEO — Mar. 1990 – Nov. 1991
GlycoGen Inc.

Vice President, Research — Apr. 1984 – Mar. 1990
Genencor International Inc.

Senior Scientist — Sep. 1978 – Apr. 1984
Department of Molecular Biology, Genentech Inc.

Assistant Professor — Nov. 1977 – Aug. 1978
Department of Molecular Genetics, University of Leiden, the Netherlands

Other professional activities

Director, Epoch BioSciences, Inc., Bothel, WA, USA
Director, PepScan, B.V., the Netherlands
Chairman, Scientific Advisory Board of Guava Technologies, Inc., Burlingame, CA, USA
Adviser, Crucell, N.V., Leiden, the Netherlands
Adviser, Abingworth Management, Inc., Palo Alto, CA, USA

Publications
49 Research Papers;
24 Issued US Patents

List of Publications

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. NO.	Title
3,174	Bacterial polypeptide expression employing tryptophan promoter-operator
1,415	Methods of producing immunoglobulins, vectors and transformed host cells for use therein
4,891	Apparatus and method for concurrent chemical synthesis
0,552	Production of recombinant polypeptides by bovine species and transgenic methods
5,725	Production of recombinant polypeptides by bovine species and transgenic methods
7,100	Oligonucleotide arrays
3,857	Transgenic bovines and milk from transgenic bovines
3,808	Bacterial polypeptide expression employing tryptophan promoter-operator
5,745	Human growth hormone
5,093	Tissue plasminogen activator variants
,957	Transgenic bovine
5,134	Tissue plasminogen activator variants
4,372	Tissue plasminogen activator variants
,076	Method of producing a transgenic bovine or transgenic bovine embryo
,529	DNA for expression of bovine growth hormone
,199	Human growth hormone
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,980	Microbial expression of a gene for human growth hormone
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Distribution:

ernal Correspondence

March 5, 1984

Genentech Employees

Bob Swanson Bob

Herb Heyneker

I am pleased to inform you that Herb Heyneker has accepted the position of Vice President of Research at Genencor, our joint venture with Corning Glass Works. Herb will continue his work at Genentech through April, during a transition period.

While he will no longer be involved in Genentech's scientific efforts, Herb is not really leaving us and will not be far away. I'm sure we'll still be seeing a lot of him, as he guides Genencor's research and provides an interface between the joint venture and ourselves.

Herb was among our very first scientists at Genentech, joining the company in 1978. He has contributed significantly to our research efforts, from the early work on somatostatin and human insulin to recent activities on plasminogen activators. At Genencor he will be overseeing the development of enzymes for food technology and chemical industry applications.

Please join me in congratulating Herb on his new position at Genencor.

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